

**SUBSTITUTED-TRIAZOLOPYRIMIDINES AS ANTICANCER AGENTS**

5                   Background of the Invention

Cross Reference to Related Applications

This application claims benefit of U.S. Provisional Appl. No. 60/215,585, which was filed June 30, 2000. This application is herein incorporated by reference.

10                  Field of the Invention

The present invention relates to a method of treating or inhibiting the growth of cancerous tumour cells and associated diseases in a mammal by administering an effective amount of a substituted-triazolopyrimidine derivative and pharmaceutically acceptable salts thereof. Further, the present invention relates to a method for the treatment or prevention of (MDR) multiple drug resistance in a mammal in need thereof which method comprises administering to said mammal an effective amount of a substituted triazolopyrimidine derivative or a pharmaceutically acceptable salt thereof. More specifically, the present invention relates to a method of treating or inhibiting the growth of cancerous tumour cells and associated diseases in a mammal by interacting with tubulin and microtubules and promotion of microtubule polymerization which comprises administering to said mammal an effective amount of a substituted-triazolopyrimidine derivative and pharmaceutically acceptable salts thereof.

25                  b) Description of the Prior Art

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Most of the cytostatics in use today either inhibit the formation of essential precursors for biosynthesis of DNA or block DNA polymerases or interfere with the template function of DNA because DNA was the primary target for developing therapeutic drugs for chemotherapy. Unfortunately,

- 5 inhibition of the formation of essential precursors for biosynthesis of DNA or blocking DNA polymerases or interference with the template function of DNA also affects normal tissues.

Microtubules are among the cellular structures necessary for cell growth. Tubulin is the biochemical target for several anticancer drugs, which

- 10 include the vinca alkaloids vincristine and vinblastine. The interaction of vincristine and vinblastine by binding to the alpha and beta-tubulin subunits interfere with the growing and shortening of the microtubules and prevents the formation of microtubules necessary for cell functions. While these compounds have efficacy in cancer chemotherapy, they also have a  
15 destabilizing effect on the microtubules which also affects rapidly proliferating normal tissues and leads to toxicity.

Paclitaxel and its semisynthetic derivative docetaxel (Taxotere®) also interfere with microtubule formation and stabilise microtubules. Paclitaxel (Taxol®), is a diterpene isolated from the bark of the Western (Pacific) yew,

- 20 *Taxus brevifolia* and is representative of a new class of therapeutic agent having a taxane ring system. It was additionally found in other members of the Taxaceae family including the yew of Canada (*Taxus canadensis*) found in Gaspesia, eastern Canada and *Taxus baccata* found in Europe whose needles contain paclitaxel and analogs and hence provide a renewable  
25 source of paclitaxel and derivatives. The crude extract was tested for the first time during the 1960s and its active principle was isolated in 1971 and the chemical structure identified (M.C. Wani et al, J.Am.Chem.Soc., 93, 2325 (1971)). Further, a wide range of activity over melanoma cells, leukemia, various carcinomas, sarcomas and non-Hodgkin lymphomas as well as a

number of solid tumors in animals was shown through additional testing.

Paclitaxel and its analogs have been produced by partial synthesis from 10-deacetylbaccatin III, a precursor obtained from yew needles and twigs, and by total synthesis (Holton, et al., J. Am. Chem. Soc. 116:1597-1601 (1994) and

- 5 Nicolaou, et al., Nature 367:630-634 (1994)). Paclitaxel has been demonstrated to possess antineoplastic activity. More recently, it was shown that the antitumor activity of paclitaxel is due to a promotion of microtubule polymerization (Kumar, N., J. Biol. Chem. 256:10435-10441 (1981); Rowinsky, et al., J. Natl. Cancer Inst., 82:1247-1259 (1990); and Schiff, et al.,  
10 Nature, 277:665-667 (1979)). Paclitaxel has now demonstrated efficacy in several human tumors in clinical trials (McGuire, et al., Ann. Int. Med., 111:273-279 (1989); Holmes, et al., J. Natl. Cancer Inst., 83:1797-1805 (1991); Kohn et al., J. Natl. Cancer Inst., 86:18-24 (1994); and A. Bicker et al., Anti-Cancer Drugs, 4,141-148 (1993)

- 15 Paclitaxel is a microtubule blocker, inhibiting mitosis by interaction with microtubules. Paclitaxel does not prevent tubulin assembly but rather accelerates tubulin polymerization and stabilizes the assembled microtubules. Paclitaxel acts in a unique way which consists in binding to microtubules, preventing their depolymerization under conditions where usually  
20 depolymerization occurred(dilution, calcium, cold and microtubules disrupting drugs). Paclitaxel blocks the cell cycle at prophase which results in an accumulation of cells in G2+M.

- Accordingly, there is still a need in the art for cytotoxic agents for use in cancer therapy. In particular, there is a need for drugs which inhibit or treat  
25 the growth of tumors which have an effect similar to paclitaxel and interfere with the process of microtubule formation. Additionally, there is a need in the art for agents which accelerate tubulin polymerization and stabilize the assembled microtubules.

Accordingly, it would be advantageous to provide a method of treating or inhibiting cell proliferation, neoplastic growth and malignant tumor growth in mammals by administering compounds which have paclitaxel like anticancer activity.

5 Additionally, it would be advantageous to provide a method for treating or inhibiting multiple drug resistance (MDR).

Substituted triazolopyrimidine compounds of this invention are known to the art and have found use in agriculture as fungicides. The preparation of compounds of this invention and methods of preparation are disclosed in the  
10 following United States Patent Numbers: 5,593,996; 5,756,509; 5,948,783; 5,981,534; 5,612,345; 5,994,360; 6,020,338; 5,985,883; 5,854,252; 5,808,066; 5,817,663; 5,955,252; 5,965,561; 5,986,135 ; and 5,750,766.

Compounds of this invention are also prepared according to procedures described in the following International Publication Numbers:  
15 WO98/46607; WO98/46608; WO99/48893; WO99/41255; EPO 834513A2; EPO 782997A2; EPO 550113B1; EPO 613900B1; FR2784381A1; EPO 989130A1; WO98/41496; WO94/20501; EPO 945453A1; EPO 562615A1 and EPO 562615B1.

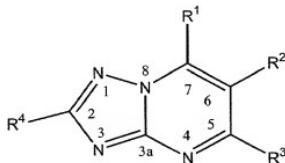
20 Summary of the Invention

A first object of the present invention is to provide a method of treating or inhibiting the growth of cancerous tumour cells and associated diseases in a mammal by administering an effective amount of a substituted-triazolopyrimidine derivative and pharmaceutically acceptable salts thereof.

25 A second object of the present invention is to provide a method of treating or inhibiting the growth of cancerous tumour cells and associated diseases in a mammal in need thereof by interacting with tubulin and

microtubules by promotion of microtubule polymerization which comprises administering to said mammal an effective amount of a substituted-triazolopyrimidine derivative and pharmaceutically acceptable salts thereof.

A third object of the present invention is to provide a method of treating or inhibiting the growth of cancerous tumour cells and associated diseases in a mammal in need thereof by administering to said mammal an effective amount of a compound of Formula (I):



(I)

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wherein:

R<sup>1</sup> is selected from the group consisting of halogen, an optionally substituted alkyl of 1 to 12 carbon atoms, optionally substituted alkenyl of 2 to 12 carbon atoms, optionally substituted alkynyl of 2 to 12 carbon atoms, optionally substituted alkadienyl of 4 to 12 carbon atoms, alkoxy of 1 to 12 carbon atoms, optionally substituted aryl of 6, 10 or 14 carbon atoms, -CN, hydroxy, halogen, carbamoyl, carboxy, alkoxy carbonyl of 2 to 12 carbon atoms, heterocyclyl, optionally substituted bicycloalkyl of 5 to 10 carbon atoms, 15 optionally substituted cycloalkyl of 3 to 8 carbon atoms in which one -CH<sub>2</sub>- may also be replaced by -O-, -S-, or -NR' where R' is H or an alkyl group of 1 to 12 carbon atoms, thiophene, optionally substituted cycloalkenyl of 5 to 10 20 carbon atoms,

carbon atoms in which one  $-\text{CH}_2-$  may also be replaced by  $-\text{O}-$ ,  $-\text{S}-$ , or  $-\text{NR}'$  where R' is H or an alkyl group of 1 to 12 carbon atoms, -S-aryl of 6, 10 or 14 carbon atoms, -S-alkyl of 1 to 12 carbon atoms, -S-cycloalkyl of 3 to 8 carbon atoms, -S-alkenyl of 2 to 12 carbon atoms, -SO<sub>2</sub>aryl of 6, 10 or 14 carbon atoms, -SO<sub>2</sub>cycloalkyl of 3 to 8 carbon atoms, -SO<sub>2</sub>alkyl of 1 to 12 carbon atoms, -O-aryl of 6, 10 or 14 carbon atoms, and the moiety  $-\text{NR}^a\text{R}^b$ ;

- 5       $\text{R}^a$  is H, optionally substituted alkyl of 1 to 12 carbon atoms, optionally substituted alkenyl of 2 to 12 carbon atoms, optionally substituted alkynyl of  
10     2 to 12 carbon atoms, optionally substituted alkadienyl of 4 to 12 carbon atoms, optionally substituted cycloalkyl of 3 to 8 carbon atoms, in which one  $-\text{CH}_2-$  may also be replaced by  $-\text{O}-$ ,  $-\text{S}-$ , or  $-\text{NR}'$  where R' is H or an alkyl group of 1 to 12 carbon atoms, optionally substituted cycloalkenyl of 5 to 10 carbon atoms, in which one  $-\text{CH}_2-$  may also be replaced by  $-\text{O}-$ ,  $-\text{S}-$ , or  $-\text{NR}'$  where R' is H or an alkyl group of 1 to 12 carbon atoms, optionally substituted bicycloalkyl of 5 to 10 carbon atoms, optionally substituted tricycloalkyl, haloalkyl of 1 to 10 carbon atoms, aryl of 6, 10 or 14 carbon atoms, heterocyclyl, benzyl, optionally substituted benzyl, cycloalkyl of 3 to 8 carbon atoms or a 3- to 6-membered heterocyclyl ring, optionally ortho-fused with an  
15     20    optionally substituted phenyl ring;

- 25       $\text{R}^b$  is H, an optionally substituted alkyl of 1 to 12 carbon atoms, optionally substituted alkenyl of 2 to 12 carbon atoms, optionally substituted alkynyl of 2 to 12 carbon atoms, optionally substituted alkadienyl of 4 to 12 carbon atoms, optionally substituted aryl of 6, 10 or 14 carbon atoms, optionally substituted

bicycloalkyl of 5 to 10 carbon atoms, optionally substituted cycloalkyl of 3 to 10 carbon atoms in which one  $-\text{CH}_2-$  may also be replaced by  $-\text{O}-$ ,  $-\text{S}-$ , or  $-\text{NR}'$  where R' is H or an alkyl group of 1 to 12 carbon atoms, optionally substituted cycloalkenyl of 5 to 10 carbon atoms in which one  $-\text{CH}_2-$  may also

- 5 be replaced by  $-\text{O}-$ ,  $-\text{S}-$ , or  $-\text{NR}'$  where R' is H or an alkyl group of 1 to 12 carbon atoms,  $-\text{S-aryl}$  of 6, 10 or 14 carbon atoms,  $-\text{S-alkyl}$ ,  $-\text{S-alkenyl}$ ,  $-\text{SO}_2\text{aryl}$  of 6, 10 or 14 carbon atoms,  $-\text{SO}_2\text{cycloalkyl}$ ,  $-\text{SO}_2\text{alkyl}$ ,  $-\text{O-aryl}$  of 6, 10 or 14 carbon atoms, heterocyclyl, benzyl, optionally substituted benzyl, cycloalkyl of 3 to 8 carbon atoms or a 3- to 6-membered heterocyclyl ring,
- 10 optionally ortho-fused with an optionally substituted phenyl ring ;  $\text{R}^a\text{R}^b$  together with the nitrogen atom to which each is attached represent an optionally substituted saturated or unsaturated heterocyclyl ring from 3 to 12 ring atoms in which optionally, at least one  $-\text{CH}_2-$  may optionally be replaced by  $-\text{O}-$ ,  $-\text{S}-$ , or  $-\text{NR}'$  where R' is H or an alkyl group of 1 to 12 carbon atoms, said saturated or unsaturated heterocyclyl ring may optionally be aryl or cycloalkyl fused;

- $\text{R}^2$  is H, optionally substituted alkyl of 1 to 12 carbon atoms, amino, hydroxy, alkylthio of 1 to 12 carbon atoms, cyano, carbamoyl, optionally substituted alkoxy of 1 to 12 carbon atoms, optionally substituted cycloalkyl of 3 to 8 carbon atoms, optionally substituted aryl of 6, 10 or 14 carbon atoms, carboxy, alkoxy carbonyl of 2 to 12 carbon atoms, aryloxy, benzyloxy, thieryl, heterocyclyl or halogen;
- 20  $\text{R}^3$  is H, halogen, alkyl of 1 to 12 carbon atoms, alkoxy of 1 to 12 carbon atoms, aryloxy,  $-\text{NR}^c\text{R}^d$ , benzyloxy, aralkyloxy, haloalkoxy of 1 to 12 carbon atoms, alkylthio of 1 to 12 carbon atoms, heterocyclyl, aryl, hydroxy,
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carbamoyl, carboxy, alkoxy carbonyl of 2 to 12 carbon atoms, cyano, amino, alkylamino of 1 to 12 carbon atoms, dialkylamino of 1 to 12 carbon atoms, or -N<sub>3</sub>;

- 5 R<sup>c</sup> is H, amino, optionally substituted alkyl of 1 to 12 carbon atoms, haloalkyl of 1 to 10 carbon atoms, optionally substituted alkenyl of 2 to 12 carbon atoms, optionally substituted alkynyl of 2 to 12 carbon atoms, optionally substituted alkadienyl of 4 to 12 carbon atoms, optionally substituted cycloalkyl of 3 to 10 carbon atoms, in which one -CH<sub>2</sub>- may also be replaced by -O-, -S-, or -NR' where R' is H or an alkyl group of 1 to 12 carbon atoms
- 10 10 optionally substituted cycloalkenyl of 5 to 10 carbon atoms, in which one -CH<sub>2</sub>- may also be replaced by -O-, -S-, or -NR' where R' is H or an alkyl group of 1 to 12 carbon atoms, optionally substituted bicycloalkyl of 5 to 10 carbon atoms, aryl of 6, 10 or 14 carbon atoms, benzyl, optionally substituted benzyl, or heterocyclyl;
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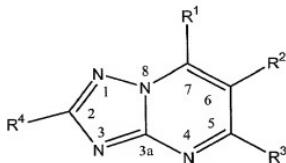
- R<sup>d</sup> is H, amino, optionally substituted alkyl of 1 to 12 carbon atoms, haloalkyl of 1 to 10 carbon atoms, optionally substituted alkenyl of 2 to 12 carbon atoms, optionally substituted alkynyl of 2 to 12 carbon atoms, optionally substituted alkadienyl of 4 to 12 carbon atoms, optionally substituted cycloalkyl of 3 to 10 carbon atoms, in which one -CH<sub>2</sub>- may also be replaced by -O-, -S-, or -NR' where R' is H or an alkyl group of 1 to 12 carbon atoms optionally substituted cycloalkenyl of 5 to 10 carbon atoms, in which one -CH<sub>2</sub>- may also be replaced by -O-, -S-, or -NR' where R' is H or an alkyl group of 1 to 12 carbon atoms optionally substituted bicycloalkyl of 5 to 10 carbon atoms, aryl of 6, 10 or 14 carbon atoms, benzyl, optionally substituted benzyl, or heterocyclyl;

- 30 R<sup>c</sup>R<sup>d</sup> together with the nitrogen atom to which each is attached represent an optionally substituted heterocyclyl ring from 3 to 8 ring atoms optionally

substituted in which one  $-\text{CH}_2-$  may also be replaced by  $-\text{O}-$ ,  $-\text{S}-$ , or  $-\text{NR}'$  where  $\text{R}'$  is H or alkyl of 1 to 12 carbon atoms;

- $\text{R}^4$  is H, optionally substituted alkyl of 1 to 12 carbon atoms, optionally
- 5 substituted alkoxy of 1 to 12 carbon atoms, amino, alkyl amino of 1 to 12 carbon atoms, dialkylamino of 1 to 12 carbon atoms, alkylthio of 1 to 12 carbon atoms, halogen, cyano, carboxy, alkoxy carbonyl of 2 to 12 carbon atoms, heterocyclyl, halogen, carbamoyl, optionally substituted aryl of 6, 10 or 14 carbon atoms, or  $-\text{CF}_3$ ;
- 10 provided that when: a)  $\text{R}^1$  is diethylamino,  $\text{R}^3$  is chloro,  $\text{R}^4$  is hydrogen,  $\text{R}^2$  is not 4-trifluoromethylphenyl, 3,4-dichlorophenyl, 4-chlorophenyl, 3-chloro-4-methoxyphenyl; b)  $\text{R}^1$  is diethylamino,  $\text{R}^3$  is bromo,  $\text{R}^4$  is hydrogen,  $\text{R}^2$  is not 4-trifluoromethylphenyl; c)  $\text{R}^1$  is isopropylamino,  $\text{R}^3$  is chloro,  $\text{R}^4$  is hydrogen,  $\text{R}^2$  is not 2-benzyloxyphenyl or 3,4,5-trimethoxyphenyl; d)  $\text{R}^1$  is
- 15 cyclopentylamino,  $\text{R}^3$  is chloro,  $\text{R}^4$  is hydrogen,  $\text{R}^2$  is not 3,4,5-trimethoxyphenyl, 2-naphthyl or 2-stilbene; e)  $\text{R}^1$  is 2-amino-bicyclo(2.2.1.)heptyl,  $\text{R}^3$  is chloro,  $\text{R}^4$  is hydrogen,  $\text{R}^2$  is not 3,4,5-trimethoxyphenyl and f)  $\text{R}^1$  is diethylamino,  $\text{R}^3$  is chloro,  $\text{R}^4$  is hydrogen,  $\text{R}^2$  is not 4-trifluoromethylphenyl and g)  $\text{R}^1$  is 1,1,1-trifluoroethoxy,  $\text{R}^3$  is chloro,  $\text{R}^4$
- 20 is hydrogen,  $\text{R}^2$  is not 2-chloro-6-fluorophenyl h)  $\text{R}^1$  is  $-\text{SO}_2\text{ethyl}$  or  $-\text{SO}_2\text{cyclopentyl}$ ,  $\text{R}^3$  is chloro,  $\text{R}^4$  is hydrogen,  $\text{R}^2$  is not 2-chloro-6-fluorophenyl; i)  $\text{R}^4$  is hydrogen,  $\text{R}^2$  is 2-chloro-6-fluorophenyl,  $\text{R}^1$  and  $\text{R}^3$  are not 1,2,4-triazole; j)  $\text{R}^1$  is cyclohexyl,  $\text{R}^4$  is hydrogen,  $\text{R}^2$  is 2,4,6-trifluorophenyl, and  $\text{R}^3$  is not  $-\text{OCH}_2\text{O}_2\text{C}(\text{CH}_3)_3$ ; k)  $\text{R}^1$  is 2-thienyl,  $\text{R}^4$
- 25 is ethyl,  $\text{R}^3$  is hydrogen and  $\text{R}^2$  is not 2-methoxyphenyl, 4-methoxyphenyl, and 4-trifluorophenyl; l)  $\text{R}^2$  is phenyl,  $\text{R}^3$  is chloro,  $\text{R}^4$  is hydrogen,  $\text{R}^1$  is not (2E)-,7-dimethyl-2,6-octadienyl  
or a pharmaceutically acceptable salt thereof.

A fourth object of the present invention is to provide a method of treating or inhibiting the growth of cancerous tumour cells and associated diseases in a mammal in need thereof by interacting with tubulin and microtubules by promotion of microtubule polymerization which comprises  
5 administering to said mammal an effective amount of a compound of Formula (I):



(I)

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wherein:

- R<sup>1</sup> is selected from the group consisting of halogen, an optionally substituted alkyl of 1 to 12 carbon atoms, optionally substituted alkenyl of 2 to 12 carbon atoms, optionally substituted alkynyl of 2 to 12 carbon atoms, optionally substituted alkadienyl of 4 to 12 carbon atoms, alkoxy of 1 to 12 carbon atoms, optionally substituted aryl of 6, 10 or 14 carbon atoms, -CN, hydroxy, halogen, carbamoyl, carboxy, alkoxy carbonyl of 2 to 12 carbon atoms, heterocycl, optionally substituted bicycloalkyl of 5 to 10 carbon atoms, optionally substituted cycloalkyl of 3 to 8 carbon atoms in which one -CH<sub>2</sub>-  
15 may also be replaced by -O-, -S-, or -NR' where R' is H or an alkyl group of 1 to 12 carbon atoms, thiophene, optionally substituted cycloalkenyl of 5 to 10 carbon atoms in which one -CH<sub>2</sub>- may also be replaced by -O-, -S-, or -NR' where R' is H or an alkyl group of 1 to 12 carbon atoms, -S-aryl of 6, 10  
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or 14 carbon atoms, -S-alkyl of 1 to 12 carbon atoms, -S-cycloalkyl of 3 to 8 carbon atoms, -S-alkenyl of 2 to 12 carbon atoms, -SO<sub>2</sub>aryl of 6, 10 or 14 carbon atoms, -SO<sub>2</sub>cycloalkyl of 3 to 8 carbon atoms, -SO<sub>2</sub>alkyl of 1 to 12 carbon atoms, -O-aryl of 6, 10 or 14 carbon atoms, and the moiety -NR<sup>a</sup>R<sup>b</sup>;

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R<sup>a</sup> is H, optionally substituted alkyl of 1 to 12 carbon atoms, optionally substituted alkenyl of 2 to 12 carbon atoms, optionally substituted alkynyl of 2 to 12 carbon atoms, optionally substituted alkadienyl of 4 to 12 carbon atoms, optionally substituted cycloalkyl of 3 to 8 carbon atoms, in which one

10 -CH<sub>2</sub>- may also be replaced by -O-, -S-, or -NR' where R' is H or an alkyl group of 1 to 12 carbon atoms, optionally substituted cycloalkenyl of 5 to 10 carbon atoms, in which one -CH<sub>2</sub>- may also be replaced by -O-, -S-, or -NR' where R' is H or an alkyl group of 1 to 12 carbon atoms, optionally substituted bicycloalkyl of 5 to 10 carbon atoms, optionally substituted tricycloalkyl,

15 haloalkyl of 1 to 10 carbon atoms, aryl of 6, 10 or 14 carbon atoms, heterocyclyl, benzyl, optionally substituted benzyl, cycloalkyl of 3 to 8 carbon atoms or a 3- to 6-membered heterocyclyl ring, optionally ortho-fused with an optionally substituted phenyl ring;

20 R<sup>b</sup> is H, an optionally substituted alkyl of 1 to 12 carbon atoms, optionally substituted alkenyl of 2 to 12 carbon atoms, optionally substituted alkynyl of 2 to 12 carbon atoms, optionally substituted alkadienyl of 4 to 12 carbon atoms, optionally substituted aryl of 6, 10 or 14 carbon atoms, optionally substituted bicycloalkyl of 5 to 10 carbon atoms, optionally substituted cycloalkyl of 3 to

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10 carbon atoms in which one  $-\text{CH}_2-$  may also be replaced by  $-\text{O}-$ ,  $-\text{S}-$ , or  $-\text{NR}'$  where R' is H or an alkyl group of 1 to 12 carbon atoms, optionally substituted cycloalkenyl of 5 to 10 carbon atoms in which one  $-\text{CH}_2-$  may also be replaced by  $-\text{O}-$ ,  $-\text{S}-$ , or  $-\text{NR}'$  where R' is H or an alkyl group of 1 to 12

- 5 carbon atoms,  $-\text{S-aryl}$  of 6, 10 or 14 carbon atoms,  $-\text{S-alkyl}$ ,  $-\text{S-alkenyl}$ ,  $-\text{SO}_2\text{aryl}$  of 6, 10 or 14 carbon atoms,  $-\text{SO}_2\text{cycloalkyl}$ ,  $-\text{SO}_2\text{alkyl}$ ,  $-\text{O-aryl}$  of 6, 10 or 14 carbon atoms, heterocyclyl, benzyl, optionally substituted benzyl, cycloalkyl of 3 to 8 carbon atoms or a 3- to 6-membered heterocyclyl ring, optionally ortho-fused with an optionally substituted phenyl ring ;

- 10  $\text{R}^a\text{R}^b$  together with the nitrogen atom to which each is attached represent an optionally substituted saturated or unsaturated heterocyclyl ring from 3 to 12 ring atoms in which optionally, at least one  $-\text{CH}_2-$  may optionally be replaced by  $-\text{O}-$ ,  $-\text{S}-$ , or  $-\text{NR}'$  where R' is H or an alkyl group of 1 to 12 carbon atoms, said saturated or unsaturated heterocyclyl ring may optionally be aryl or cycloalkyl fused;

- 20  $\text{R}^2$  is H, optionally substituted alkyl of 1 to 12 carbon atoms, amino, hydroxy, alkylthio of 1 to 12 carbon atoms, cyano, carbamoyl, optionally substituted alkoxy of 1 to 12 carbon atoms, optionally substituted cycloalkyl of 3 to 8 carbon atoms, optionally substituted aryl of 6, 10 or 14 carbon atoms, carboxy, alkoxy carbonyl of 2 to 12 carbon atoms, aryloxy, benzyloxy, thienyl, heterocyclyl or halogen;

- 25  $\text{R}^3$  is H, halogen, alkyl of 1 to 12 carbon atoms, alkoxy of 1 to 12 carbon atoms, aryloxy,  $-\text{NR}^c\text{R}^d$ , benzyloxy, aralkyloxy, haloalkoxy of 1 to 12 carbon atoms, alkylthio of 1 to 12 carbon atoms, heterocyclyl, aryl, hydroxy, carbamoyl, carboxy, alkoxy carbonyl of 2 to 12 carbon atoms, cyano, amino,

alkylamino of 1 to 12 carbon atoms, dialkylamino of 1 to 12 carbon atoms, or -N<sub>3</sub>;

- R<sup>c</sup> is H, amino, optionally substituted alkyl of 1 to 12 carbon atoms, haloalkyl of 1 to 10 carbon atoms, optionally substituted alkenyl of 2 to 12 carbon atoms, optionally substituted alkynyl of 2 to 12 carbon atoms, optionally substituted alkadienyl of 4 to 12 carbon atoms, optionally substituted cycloalkyl of 3 to 10 carbon atoms, in which one -CH<sub>2</sub>- may also be replaced by -O-, -S-, or -NR' where R' is H or an alkyl group of 1 to 12 carbon atoms optionally substituted cycloalkenyl of 5 to 10 carbon atoms, in which one -CH<sub>2</sub>- may also be replaced by -O-, -S-, or -NR' where R' is H or an alkyl group of 1 to 12 carbon atoms optionally substituted bicycloalkyl of 5 to 10 carbon atoms, aryl of 6, 10 or 14 carbon atoms, benzyl, optionally substituted benzyl, heterocyclyl;
- R<sup>d</sup> is H, amino, optionally substituted alkyl of 1 to 12 carbon atoms, haloalkyl of 1 to 10 carbon atoms, optionally substituted alkenyl of 2 to 12 carbon atoms, optionally substituted alkynyl of 2 to 12 carbon atoms, optionally substituted alkadienyl of 4 to 12 carbon atoms, optionally substituted cycloalkyl of 3 to 10 carbon atoms, in which one -CH<sub>2</sub>- may also be replaced by -O-, -S-, or -NR' where R' is H or an alkyl group of 1 to 12 carbon atoms optionally substituted cycloalkenyl of 5 to 10 carbon atoms, in which one -CH<sub>2</sub>- may also be replaced by -O-, -S-, or -NR' where R' is H or an alkyl group of 1 to 12 carbon atoms optionally substituted bicycloalkyl of 5 to 10 carbon atoms, aryl of 6, 10 or 14 carbon atoms, benzyl, optionally substituted benzyl, or heterocyclyl;

R<sup>c</sup>R<sup>d</sup> together with the nitrogen atom to which each is attached represent an optionally substituted heterocyclyl ring from 3 to 8 ring atoms optionally substituted in which one -CH<sub>2</sub>- may also be replaced by -O-, -S-, or -NR' where R' is H or alkyl of 1 to 12 carbon atoms;

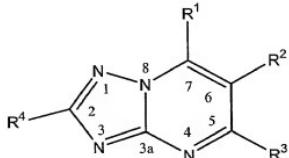
R<sup>4</sup> is H, optionally substituted alkyl of 1 to 12 carbon atoms, optionally substituted alkoxy of 1 to 12 carbon atoms, amino, alkyl amino of 1 to 12 carbon atoms, dialkylamino of 1 to 12 carbon atoms, alkylthio of 1 to 12 carbon atoms, halogen, cyano, carboxy, alkoxycarbonyl of 2 to 12 carbon atoms, heterocycl, halogen, carbamoyl, optionally substituted aryl of 6, 10 or 14 carbon atoms, or -CF<sub>3</sub>;

provided that when: a) R<sup>1</sup> is diethylamino, R<sup>3</sup> is chloro, R<sup>4</sup> is hydrogen, R<sup>2</sup> is not 4-trifluoromethylphenyl, 3,4-dichlorophenyl, 4-chlorophenyl, 3-chloro-4-methoxyphenyl; b) R<sup>1</sup> is diethylamino, R<sup>3</sup> is bromo, R<sup>4</sup> is hydrogen, R<sup>2</sup> is not 4-trifluoromethylphenyl; c) R<sup>1</sup> is isopropylamino, R<sup>3</sup> is chloro, R<sup>4</sup> is hydrogen, R<sup>2</sup> is not 2-benzylxyphenyl or 3,4,5-trimethoxyphenyl; d) R<sup>1</sup> is cyclopentylamino, R<sup>3</sup> is chloro, R<sup>4</sup> is hydrogen, R<sup>2</sup> is not 3,4,5-trimethoxyphenyl, 2-naphyl or 2-stilbene; e) R<sup>1</sup> is 2-amino-bicyclo(2.2.1.)heptyl, R<sup>3</sup> is chloro, R<sup>4</sup> is hydrogen, R<sup>2</sup> is not 3,4,5-trimethoxyphenyl and f) R<sup>1</sup> is diethylamino, R<sup>3</sup> is chloro, R<sup>4</sup> is hydrogen, R<sup>2</sup> is not 4-trifluoromethylphenyl and g) R<sup>1</sup> is 1,1,1-trifluoroethoxy, R<sup>3</sup> is chloro, R<sup>4</sup> is hydrogen, R<sup>2</sup> is not 2-chloro-6-fluorophenyl h) R<sup>1</sup> is -SO<sub>2</sub>ethyl or -SO<sub>2</sub>cyclopentyl, R<sup>3</sup> is chloro, R<sup>4</sup> is hydrogen, R<sup>2</sup> is not 2-chloro-6-fluorophenyl; i) R<sup>4</sup> is hydrogen, R<sup>2</sup> is 2-chloro-6-fluorophenyl, R<sup>1</sup> and R<sup>3</sup> are not 1,2,4-triazole; j) R<sup>1</sup> is cyclohexyl, R<sup>4</sup> is hydrogen, R<sup>2</sup> is 2,4,6-trifluorophenyl, and R<sup>3</sup> is not -OCH<sub>2</sub>O<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>; k) R<sup>1</sup> is 2-thienyl, R<sup>4</sup> is ethyl, R<sup>3</sup> is hydrogen and R<sup>2</sup> is not 2-methoxyphenyl, 4-methoxyphenyl, and 4-trifluorophenyl; l) R<sup>2</sup> is phenyl, R<sup>3</sup> is chloro, R<sup>4</sup> is hydrogen R<sup>1</sup> is not (2E)-,7-dimethyl-2,6-octadienyl or a pharmaceutically acceptable salt thereof.

A fifth object of the present invention is to provide a method for the treatment or prevention of multiple drug resistance (MDR) in a mammal in need thereof which method comprises administering to said mammal an effective amount of a substituted triazolopyrimidine derivative or a

pharmaceutically acceptable salt thereof. In particular the multiple drug resistance (MDR) is mediated by p-glycoprotein or MXR.

A sixth object of the present invention is to provide a method for the treatment or prevention of multiple drug resistance (MDR) in a mammal in  
5 need thereof by administering to said mammal an effective amount of a compound of Formula (I):



(I)

10

wherein:

- R<sup>1</sup> is selected from the group consisting of halogen, an optionally substituted alkyl of 1 to 12 carbon atoms, optionally substituted alkenyl of 2 to 12 carbon atoms, optionally substituted alkynyl of 2 to 12 carbon atoms, optionally  
15 substituted alkadienyl of 4 to 12 carbon atoms, alkoxy of 1 to 12 carbon atoms, optionally substituted aryl of 6, 10 or 14 carbon atoms, -CN, hydroxy, halogen, carbamoyl, carboxy, alkoxy carbonyl of 2 to 12 carbon atoms, heterocycl, optionally substituted bicycloalkyl of 5 to 10 carbon atoms, optionally substituted cycloalkyl of 3 to 8 carbon atoms in which one -CH<sub>2</sub>-  
20 may also be replaced by -O-, -S-, or -NR' where R' is H or an alkyl group of 1 to 12 carbon atoms, thiophene, optionally substituted cycloalkenyl of 5 to 10 carbon atoms in which one -CH<sub>2</sub>- may also be replaced by -O-, -S-, or

- NR' where R' is H or an alkyl group of 1 to 12 carbon atoms, -S-aryl of 6, 10 or 14 carbon atoms, -S-alkyl of 1 to 12 carbon atoms, -S-cycloalkyl of 3 to 8 carbon atoms, -S-alkenyl of 2 to 12 carbon atoms, -SO<sub>2</sub>aryl of 6, 10 or 14 carbon atoms, -SO<sub>2</sub>cycloalkyl of 3 to 8 carbon atoms, -SO<sub>2</sub>alkyl of 1 to 12 carbon atoms, -O-aryl of 6, 10 or 14 carbon atoms, and the moiety -NR<sup>a</sup>R<sup>b</sup>;
- 5 R<sup>a</sup> is H, optionally substituted alkyl of 1 to 12 carbon atoms, optionally substituted alkenyl of 2 to 12 carbon atoms, optionally substituted alkynyl of 2 to 12 carbon atoms, optionally substituted alkadienyl of 4 to 12 carbon atoms, 10 optionally substituted cycloalkyl of 3 to 8 carbon atoms, in which one -CH<sub>2</sub>- may also be replaced by -O-, -S-, or -NR' where R' is H or an alkyl group of 1 to 12 carbon atoms, optionally substituted cycloalkenyl of 5 to 10 carbon atoms, in which one -CH<sub>2</sub>- may also be replaced by -O-, -S-, or -NR' where R' is H or an alkyl group of 1 to 12 carbon atoms, optionally substituted 15 bicycloalkyl of 5 to 10 carbon atoms, optionally substituted tricycloalkyl, haloalkyl of 1 to 10 carbon atoms, aryl of 6, 10 or 14 carbon atoms, heterocycl, benzyl, optionally substituted benzyl, cycloalkyl of 3 to 8 carbon atoms or a 3- to 6-membered heterocycl ring, optionally ortho-fused with an optionally substituted phenyl ring;
- 20 R<sup>b</sup> is H, an optionally substituted alkyl of 1 to 12 carbon atoms, optionally substituted alkenyl of 2 to 12 carbon atoms, optionally substituted alkynyl of 2 to 12 carbon atoms, optionally substituted alkadienyl of 4 to 12 carbon atoms, optionally substituted aryl of 6, 10 or 14 carbon atoms, optionally substituted 25 bicycloalkyl of 5 to 10 carbon atoms, optionally substituted cycloalkyl of 3 to

- 10 carbon atoms in which one  $-\text{CH}_2-$  may also be replaced by  $-\text{O}-$ ,  $-\text{S}-$ , or  
 $-\text{NR}'$  where  $\text{R}'$  is H or an alkyl group of 1 to 12 carbon atoms, optionally  
substituted cycloalkenyl of 5 to 10 carbon atoms in which one  $-\text{CH}_2-$  may also  
be replaced by  $-\text{O}-$ ,  $-\text{S}-$ , or  $-\text{NR}'$  where  $\text{R}'$  is H or an alkyl group of 1 to 12
- 5 carbon atoms,  $-\text{S-aryl}$  of 6, 10 or 14 carbon atoms,  $-\text{S-alkyl}$ ,  $-\text{S-alkenyl}$ ,  
 $-\text{SO}_2\text{aryl}$  of 6, 10 or 14 carbon atoms,  $-\text{SO}_2\text{cycloalkyl}$ ,  $-\text{SO}_2\text{alkyl}$ ,  $-\text{O-aryl}$  of 6,  
10 or 14 carbon atoms, heterocyclyl, benzyl, optionally substituted benzyl,  
cycloalkyl of 3 to 8 carbon atoms or a 3- to 6-membered heterocyclyl ring,  
optionally ortho-fused with an optionally substituted phenyl ring ;
- 10  $\text{R}^a\text{R}^b$  together with the nitrogen atom to which each is attached represent an  
optionally substituted saturated or unsaturated heterocyclyl ring from 3 to 12  
ring atoms in which optionally, at least one  $-\text{CH}_2-$  may optionally be  
replaced by  $-\text{O}-$ ,  $-\text{S}-$ , or  $-\text{NR}'$  where  $\text{R}'$  is H or an alkyl group of 1 to 12 carbon  
atoms, said saturated or unsaturated heterocyclyl ring may optionally be aryl  
15 or cycloalkyl fused;
- 15  $\text{R}^2$  is H, optionally substituted alkyl of 1 to 12 carbon atoms, amino, hydroxy,  
alkylthio of 1 to 12 carbon atoms, cyano, carbamoyl, optionally substituted  
alkoxy of 1 to 12 carbon atoms, optionally substituted cycloalkyl of 3 to 8  
20 carbon atoms, optionally substituted aryl of 6, 10 or 14 carbon atoms,  
carboxy, alkoxy carbonyl of 2 to 12 carbon atoms, aryloxy, benzyloxy, thienyl,  
heterocyclyl or halogen;
- 20  $\text{R}^3$  is H, halogen, alkyl of 1 to 12 carbon atoms, alkoxy of 1 to 12 carbon  
atoms, aryloxy,  $-\text{NR}^c\text{R}^d$ , benzyloxy, aralkyloxy, haloalkoxy of 1 to 12 carbon  
atoms, alkylthio of 1 to 12 carbon atoms, heterocyclyl, aryl, hydroxy,  
carbamoyl, carboxy, alkoxy carbonyl of 2 to 12 carbon atoms, cyano, amino,

alkylamino of 1 to 12 carbon atoms, dialkylamino of 1 to 12 carbon atoms, or -N<sub>3</sub>;

- R<sup>c</sup> is H, amino, optionally substituted alkyl of 1 to 12 carbon atoms, haloalkyl of 1 to 10 carbon atoms, optionally substituted alkenyl of 2 to 12 carbon atoms, optionally substituted alkynyl of 2 to 12 carbon atoms, optionally substituted alkadienyl of 4 to 12 carbon atoms, optionally substituted cycloalkyl of 3 to 10 carbon atoms, in which one -CH<sub>2</sub>- may also be replaced by -O-, -S-, or -NR' where R' is H or an alkyl group of 1 to 12 carbon atoms optionally substituted cycloalkenyl of 5 to 10 carbon atoms, in which one -CH<sub>2</sub>- may also be replaced by -O-, -S-, or -NR' where R' is H or an alkyl group of 1 to 12 carbon atoms, optionally substituted bicycloalkyl of 5 to 10 carbon atoms, aryl of 6, 10 or 14 carbon atoms, benzyl, optionally substituted benzyl, or heterocyclyl;
- R<sup>d</sup> is H, amino, optionally substituted alkyl of 1 to 12 carbon atoms, haloalkyl of 1 to 10 carbon atoms, optionally substituted alkenyl of 2 to 12 carbon atoms, optionally substituted alkynyl of 2 to 12 carbon atoms, optionally substituted alkadienyl of 4 to 12 carbon atoms, optionally substituted cycloalkyl of 3 to 10 carbon atoms, in which one -CH<sub>2</sub>- may also be replaced by -O-, -S-, or -NR' where R' is H or an alkyl group of 1 to 12 carbon atoms optionally substituted cycloalkenyl of 5 to 10 carbon atoms, in which one -CH<sub>2</sub>- may also be replaced by -O-, -S-, or -NR' where R' is H or an alkyl group of 1 to 12 carbon atoms optionally substituted bicycloalkyl of 5 to 10 carbon atoms, aryl of 6, 10 or 14 carbon atoms, benzyl, optionally substituted benzyl, or heterocyclyl;
- R<sup>c</sup>R<sup>d</sup> together with the nitrogen atom to which each is attached represent an optionally substituted heterocyclyl ring from 3 to 8 ring atoms optionally substituted in which one -CH<sub>2</sub>- may also be replaced by -O-, -S-, or -NR' where R' is H or alkyl of 1 to 12 carbon atoms;

- R<sup>4</sup> is H, optionally substituted alkyl of 1 to 12 carbon atoms, optionally substituted alkoxy of 1 to 12 carbon atoms, amino, alkyl amino of 1 to 12 carbon atoms, dialkylamino of 1 to 12 carbon atoms, alkylthio of 1 to 12 carbon atoms, halogen, cyano, carboxy, alkoxy carbonyl of 2 to 12 carbon atoms, heterocyclyl, halogen, carbamoyl, optionally substituted aryl of 6, 10 or 14 carbon atoms, or -CF<sub>3</sub>;
- provided that when: a) R<sup>1</sup> is diethylamino, R<sup>3</sup> is chloro, R<sup>4</sup> is hydrogen, R<sup>2</sup> is not 4-trifluoromethylphenyl, 3,4-dichlorophenyl, 4-chlorophenyl, 3-chloro-4-methoxyphenyl; b) R<sup>1</sup> is diethylamino, R<sup>3</sup> is bromo, R<sup>4</sup> is hydrogen, R<sup>2</sup> is not 4-trifluoromethylphenyl; c) R<sup>1</sup> is isopropylamino, R<sup>3</sup> is chloro, R<sup>4</sup> is hydrogen, R<sup>2</sup> is not 2-benzyloxyphenyl or 3,4,5-trimethoxyphenyl; d) R<sup>1</sup> is cyclopentylamino, R<sup>3</sup> is chloro, R<sup>4</sup> is hydrogen, R<sup>2</sup> is not 3,4,5-trimethoxyphenyl, 2-naphthyl or 2-stilbene; e) R<sup>1</sup> is 2-amino-bicyclo(2.2.1.)heptyl, R<sup>3</sup> is chloro, R<sup>4</sup> is hydrogen, R<sup>2</sup> is not 3,4,5-trimethoxyphenyl and f) R<sup>1</sup> is diethylamino, R<sup>3</sup> is chloro, R<sup>4</sup> is hydrogen, R<sup>2</sup> is not 4-trifluoromethylphenyl and g) R<sup>1</sup> is 1,1,1-trifluoroethoxy, R<sup>3</sup> is chloro, R<sup>4</sup> is hydrogen, R<sup>2</sup> is not 2-chloro-6-fluorophenyl h) R<sup>1</sup> is -SO<sub>2</sub>ethyl or -SO<sub>2</sub>cyclopentyl, R<sup>3</sup> is chloro, R<sup>4</sup> is hydrogen, R<sup>2</sup> is not 2-chloro-6-fluorophenyl; i) R<sup>4</sup> is hydrogen, R<sup>2</sup> is 2-chloro-6-fluorophenyl, R<sup>1</sup> and R<sup>3</sup> are not 1,2,4-triazole; j) R<sup>1</sup> is cyclohexyl, R<sup>4</sup> is hydrogen, R<sup>2</sup> is 2,4,6-trifluorophenyl, and R<sup>3</sup> is not -OCH<sub>2</sub>O<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>; k) R<sup>1</sup> is 2-thienyl, R<sup>4</sup> is ethyl, R<sup>3</sup> is hydrogen and R<sup>2</sup> is not 2-methoxyphenyl, 4-methoxyphenyl, and 4-trifluorophenyl; l) R<sup>2</sup> is phenyl, R<sup>3</sup> is chloro, R<sup>4</sup> is hydrogen, R<sup>1</sup> is not (2E)-,7-dimethyl-2,6-octadienyl or a pharmaceutically acceptable salt thereof.

Among the preferred groups of compounds of Formula (I) including pharmaceutically acceptable salts thereof useful for the methods of this invention are those in the subgroups below wherein the other variables of Formula (I) in the subgroups are as defined above wherein:

- a) R<sup>1</sup> is selected from the group consisting of an optionally substituted alkyl of 1 to 12 carbon atoms, optionally substituted alkenyl of 2 to 12 carbon atoms, optionally substituted alkynyl of 2 to 12 carbon atoms, optionally substituted alkadienyl of 4 to 12 carbon atoms, optionally substituted aryl of 6, 10 or 14 carbon atoms, optionally substituted bicycloalkyl of 5 to 10 carbon atoms, optionally substituted cycloalkyl of 3 to 8 carbon atoms in which one –CH<sub>2</sub>– may also be replaced by –O-, -S-, or –NR' where R' is H or an alkyl group of 1 to 12 carbon atoms, optionally substituted cycloalkenyl of 5 to 10 carbon atoms in which one –CH<sub>2</sub>– may also be replaced by –O-, -S-, or –NR' where R' is H or an alkyl group of 1 to 12 carbon atoms, -S-aryl of 6, 10 or 14 carbon atoms, -S-alkyl of 1 to 12 carbon atoms, -S-alkenyl of 2 to 12 carbon atoms, -SO<sub>2</sub>aryl of 6, 10 or 14 carbon atoms, -SO<sub>2</sub>cycloalkyl of 3 to 8 carbon atoms, -SO<sub>2</sub>alkyl of 1 to 12 carbon atoms, -O-aryl of 6, 10 or 14 carbon atoms, and the moiety –NR<sup>a</sup>R<sup>b</sup>;
- b) R<sup>a</sup> and R<sup>b</sup> each independently represent the moiety –C\*H(R<sup>e</sup>)(R<sup>f</sup>) where R<sup>e</sup> and R<sup>f</sup> independently represent an optionally halo-substituted alkyl group of 1 to 12 carbon atoms where C\* represents the (R) or (S) isomer;
- c) R<sup>2</sup> is optionally substituted aryl of 6, 10 or 14 carbon atoms, aryloxy, thienyl, benzyloxy, heterocyclyl or halogen;
- d) R<sup>3</sup> is halogen, alkyl of 1 to 12 carbon atoms, alkoxy of 1 to 12 carbon atoms, aryloxy, -NR<sup>c</sup>R<sup>d</sup>, benzyloxy, aralkyloxy, haloalkoxy of 1 to 12 carbon atoms, alkylthio of 1 to 12 carbon atoms, hydroxy, cyano, amino, alkylamino of 1 to 12 carbon atoms, dialkylamino of 1 to 12 carbon atoms, or -N<sub>3</sub>;
- e) R<sup>4</sup> is H, optionally substituted alkyl of 1 to 12 carbon atoms, optionally substituted alkoxy of 1 to 12 carbon atoms, amino, alkyl amino of 1 to 12 carbon atoms, dialkylamino of 1 to 12 carbon atoms, -CF<sub>3</sub>;

Among the additionally preferred groups of compounds of this invention according to general Formula (I) including pharmaceutically acceptable salts thereof useful for the methods of this invention are those in the subgroups below, wherein the other variables of Formula (I) in the

5 subgroups are as defined above wherein:

- a) R<sup>1</sup> is selected from the group consisting of an optionally substituted alkyl of 1 to 12 carbon atoms, optionally substituted alkenyl of 2 to 12 carbon atoms, optionally substituted alkynyl of 2 to 12 carbon atoms, optionally substituted alkadienyl of 4 to 12 carbon atoms, optionally substituted aryl of 6, 10 or 14 10 carbon atoms, optionally substituted bicycloalkyl of 5 to 10 carbon atoms, optionally substituted cycloalkyl of 3 to 8 carbon atoms in which one –CH<sub>2</sub> may also be replaced by –O-, –S-, or –NR' where R' is H or an alkyl group of 1 to 12 carbon atoms, optionally substituted cycloalkenyl of 5 to 10 carbon 15 atoms in which one –CH<sub>2</sub> may also be replaced by –O-, –S-, or –NR' where R' is H or an alkyl group of 1 to 12 carbon atoms, –S-aryl of 6, 10 or 14 carbon atoms, –S-alkyl of 1 to 12 carbon atoms, –S-alkenyl of 2 to 12 carbon atoms, –SO<sub>2</sub>aryl of 6, 10 or 14 carbon atoms, –SO<sub>2</sub>cycloalkyl of 3 to 8 carbon atoms, –SO<sub>2</sub>alkyl of 1 to 12 carbon atoms, –O-aryl of 6, 10 or 14 carbon atoms, and 20 the moiety –NR<sup>a</sup>R<sup>b</sup> wherein R<sup>a</sup>R<sup>b</sup> are optionally taken together with the nitrogen to which each is attached;
- b) R<sup>2</sup> is optionally substituted aryl of 6, 10 or 14 carbon atoms or heterocyclyl;
- 25 c) R<sup>3</sup> is halogen, alkoxy of 1 to 12 carbon atoms, –NR<sup>c</sup>R<sup>d</sup>, haloalkoxy of 1 to 12 carbon atoms, alkylthio of 1 to 12 carbon atoms, cyano, amino, alkylamino of 1 to 12 carbon atoms, dialkylamino of 1 to 12 carbon atoms, or –N<sub>3</sub>;
- 30 d) R<sup>4</sup> is H, optionally substituted alkyl of 1 to 12 carbon atoms, amino, alkyl amino of 1 to 12 carbon atoms, dialkylamino of 1 to 12 carbon atoms, –CF<sub>3</sub>;

Among the more preferred groups of compounds of Formula (I) including pharmaceutically acceptable salts thereof useful for the methods of this invention are those in the subgroups below including the pharmaceutically acceptable salts thereof wherein the other variables of Formula (I) in the

5 subgroups are as defined above wherein:

a) R<sup>1</sup> is selected from the group consisting of an optionally substituted alkyl of 1 to 12 carbon atoms, optionally substituted cycloalkyl of 3 to 8 carbon atoms in which one -CH<sub>2</sub>- may also be replaced by -O-, -S-, or -NR' where R' is H

10 or an alkyl group of 1 to 12 carbon atoms, optionally substituted cycloalkenyl of 5 to 10 carbon atoms in which one -CH<sub>2</sub>- may also be replaced by -O-, -S-, or -NR' where R' is H or an alkyl group of 1 to 12 carbon atoms, -S-aryl of 6, 10 or 14 carbon atoms, -S-alkyl of 1 to 12 carbon atoms, -S-alkenyl of 2 to 12 carbon atoms, -SO<sub>2</sub>aryl of 6, 10 or 14 carbon atoms, -SO<sub>2</sub>cycloalkyl of

15 5 to 10 carbon atoms, -SO<sub>2</sub>alkyl of 1 to 12 carbon atoms, and the moiety -NR<sup>a</sup>R<sup>b</sup> wherein R<sup>a</sup>R<sup>b</sup> are optionally taken together with the nitrogen to which each is attached;

b) R<sup>2</sup> is optionally substituted aryl of 6, 10 or 14 carbon atoms;

20 c) R<sup>3</sup> is halogen, alkoxy of 1 to 12 carbon atoms, -NR<sup>c</sup>R<sup>d</sup>, haloalkoxy of 1 to 12 carbon atoms, alkylthio of 1 to 12 carbon atoms, cyano, or -N<sub>3</sub>;

d) R<sup>4</sup> is H;

25 Among the most preferred groups of compounds of Formula (I) including pharmaceutically acceptable salts thereof useful for the methods of this invention are those in the subgroups below including the pharmaceutically acceptable salts thereof wherein the other variables of Formula (I) in the

30 subgroups are as defined above wherein:

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- a) R<sup>1</sup> is selected from the group consisting of an optionally substituted cycloalkyl of 3 to 8 carbon atoms in which one –CH<sub>2</sub>- may also be replaced by –O-, –S-, or –NR' where R' is H or an alkyl group of 1 to 12 carbon atoms, optionally substituted cycloalkenyl of 5 to 10 carbon atoms in which one
  - 5    -CH<sub>2</sub>- may also be replaced by –O-, –S-, or –NR' where R' is H or an alkyl group of 1 to 12 carbon atoms, –S-aryl of 6, 10 or 14 carbon atoms, –S-alkyl of 1 to 12 carbon atoms, –S-alkenyl of 2 to 12 carbon atoms, –SO<sub>2</sub>aryl of 6, 10 or 14 carbon atoms, –SO<sub>2</sub>cycloalkyl of 3 to 8 carbon atoms, –SO<sub>2</sub>alkyl of 1 to 12 carbon atoms, and the moiety –NR<sup>a</sup>R<sup>b</sup> wherein R<sup>a</sup>R<sup>b</sup> are optionally taken
  - 10   together with the nitrogen to which each is attached; R<sup>2</sup> is optionally substituted phenyl; R<sup>3</sup> is halogen, alkoxy of 1 to 12 carbon atoms, –NR<sup>c</sup>R<sup>d</sup>, haloalkoxy of 1 to 12 carbon atoms, alkylthio of 1 to 12 carbon atoms, cyano, or –N<sub>3</sub>; R<sup>4</sup> is H;
  - 15   b) R<sup>1</sup> is the moiety –NR<sup>a</sup>R<sup>b</sup> wherein R<sup>a</sup>R<sup>b</sup> are optionally taken together with the nitrogen to which each is attached; R<sup>2</sup> is optionally substituted phenyl; R<sup>3</sup> is halogen, alkoxy of 1 to 12 carbon atoms, –NR<sup>c</sup>R<sup>d</sup>, haloalkoxy of 1 to 12 carbon atoms, alkylthio of 1 to 12 carbon atoms, cyano, or –N<sub>3</sub>; R<sup>4</sup> is H;
  - 20   c) R<sup>1</sup> is the moiety –NR<sup>a</sup>R<sup>b</sup> wherein R<sup>a</sup>R<sup>b</sup> are optionally taken together with the nitrogen to which each is attached;  
R<sup>2</sup> is optionally substituted phenyl;  
R<sup>3</sup> is halogen, alkoxy, –NR<sup>c</sup>R<sup>d</sup>, haloalkoxy of 1 to 12 carbon atoms, alkylthio of 1 to 12 carbon atoms, cyano, or –N<sub>3</sub>;
  - 25   R<sup>4</sup> is H;  
R<sup>a</sup> is H, optionally substituted alkyl of 1 to 12 carbon atoms, optionally substituted alkenyl of 2 to 12 carbon atoms, optionally substituted alkadienyl of 4 to 12 carbon atoms, optionally substituted cycloalkyl of 3 to 8 carbon

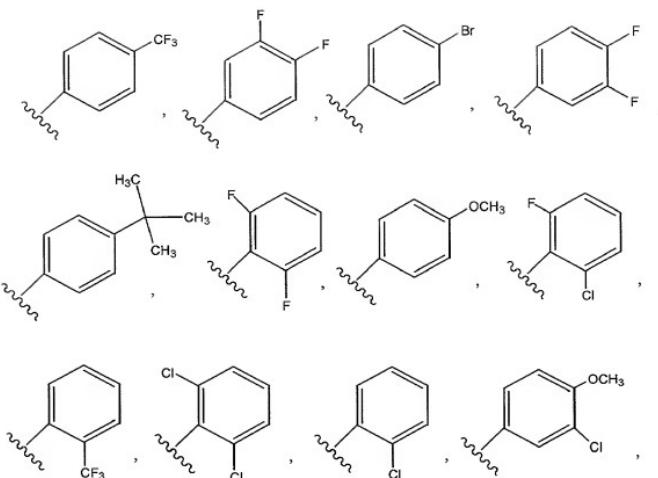
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- atoms, in which one  $-\text{CH}_2-$  may also be replaced by  $-\text{O}-$ ,  $-\text{S}-$ , or  $-\text{NR}'$  where R' is H or an alkyl group of 1 to 12 carbon atoms, optionally substituted cycloalkenyl of 5 to 10 carbon atoms, in which one  $-\text{CH}_2-$  may also be replaced by  $-\text{O}-$ ,  $-\text{S}-$ , or  $-\text{NR}'$  where R' is H or an alkyl group of 1 to 12
- 5 carbon atoms, haloalkyl of 1 to 10 carbon atoms, aryl of 6, 10 or 14 carbon atoms, heterocyclyl, benzyl, optionally substituted benzyl; R<sup>b</sup> is H, an optionally substituted alkyl of 1 to 12 carbon atoms, optionally substituted alkenyl of 2 to 12 carbon atoms, optionally substituted alkadienyl of 4 to 12 carbon atoms, optionally substituted aryl of 6, 10 or 14 carbon atoms,
- 10 optionally substituted cycloalkyl of 3 to 8 carbon atoms in which one  $-\text{CH}_2-$  may also be replaced by  $-\text{O}-$ ,  $-\text{S}-$ , or  $-\text{NR}'$  where R' is H or an alkyl group of 1 to 12 carbon atoms, optionally substituted cycloalkenyl of 5 to 10 carbon atoms in which one  $-\text{CH}_2-$  may also be replaced by  $-\text{O}-$ ,  $-\text{S}-$ , or  $-\text{NR}'$  where R' is H or an alkyl group of 1 to 12 carbon atoms,  $-\text{S-aryl}$  of 6, 10 or 14 carbon
- 15 atoms,  $-\text{S-alkyl}$  of 1 to 12 carbon atoms,  $-\text{S-alkenyl}$  of 2 to 12 carbon atoms,  $-\text{SO}_2\text{aryl}$  of 6, 10 or 14 carbon atoms,  $-\text{SO}_2\text{cycloalkyl}$  of 3 to 8 carbon atoms,  $-\text{SO}_2\text{alkyl}$  of 1 to 12 carbon atoms,  $-\text{O-aryl}$  of 6, 10 or 14 carbon atoms; R<sup>a</sup>R<sup>b</sup> together with the nitrogen atom to which each is attached represent an optionally substituted saturated or unsaturated heterocyclyl ring from 3 to 12
- 20 ring atoms in which optionally, at least one  $-\text{CH}_2-$  may also be replaced by  $-\text{O}-$ ,  $-\text{S}-$ , or  $-\text{NR}'$  where R' is H or an alkyl group of 2 to 12 carbon atoms, said saturated or unsaturated heterocyclyl ring may optionally be aryl or cycloalkyl fused;

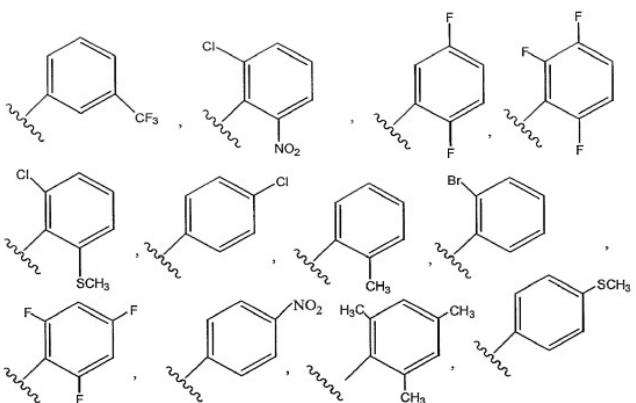
R<sup>c</sup> is H, amino, optionally substituted alkyl of 1 to 12 carbon atoms, haloalkyl of 1 to 10 carbon atoms, optionally substituted alkenyl of 2 to 12 carbon atoms, optionally substituted alkadienyl of 4 to 12 carbon atoms, optionally substituted cycloalkyl of 3 to 8 carbon atoms, in which one –CH<sub>2</sub>– may also  
5 be replaced by –O-, –S-, or –NR' where R' is H or an alkyl group of 1 to 12 carbon atoms optionally substituted cycloalkenyl of 5 to 10 carbon atoms, in which one –CH<sub>2</sub>– may also be replaced by –O-, –S-, or –NR' where R' is H or an alkyl group of 1 to 12 carbon atoms optionally substituted bicycloalkyl of 5  
10 to 10 carbon atoms, aryl of 6, 10 or 14 carbon atoms, benzyl, optionally substituted benzyl, or heterocycl;

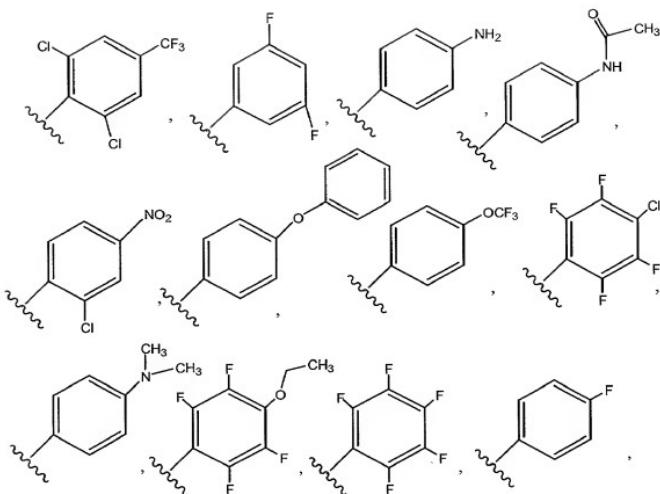
R<sup>d</sup> is H, amino, optionally substituted alkyl of 1 to 12 carbon atoms, haloalkyl of 1 to 10 carbon atoms, optionally substituted alkenyl of 2 to 12 carbon atoms, optionally substituted alkadienyl of 4 to 12 carbon atoms, optionally  
15 substituted cycloalkyl of 3 to 10 carbon atoms, in which one –CH<sub>2</sub>– may also be replaced by –O-, –S-, or –NR' where R' is H or an alkyl group of 1 to 12 carbon atoms optionally substituted cycloalkenyl of 5 to 10 carbon atoms, in which one –CH<sub>2</sub>– may also be replaced by –O-, –S-, or –NR' where R' is H or an alkyl group of 1 to 12 carbon atoms optionally substituted bicycloalkyl of 5  
20 to 10 carbon atoms, aryl of 6, 10 or 14 carbon atoms, benzyl, optionally substituted benzyl, or heterocycl;

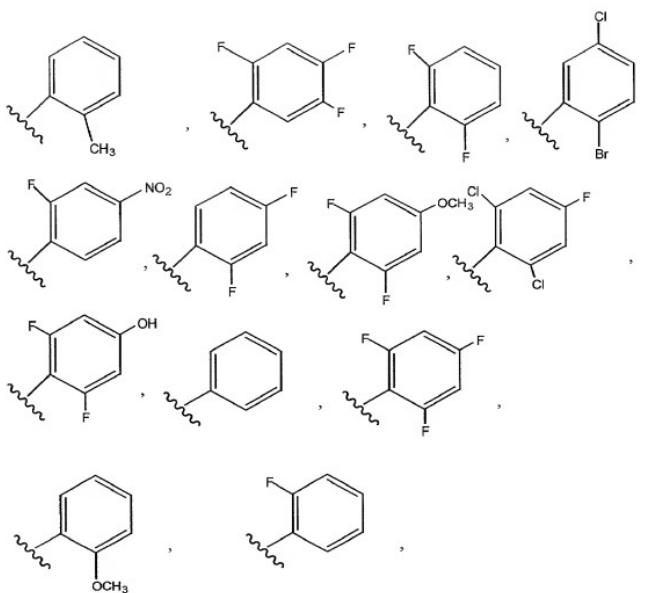
R<sup>c</sup>R<sup>d</sup> together with the nitrogen atom to which each is attached represent an optionally substituted heterocyclyl ring from 3 to 8 ring atoms optionally  
25 substituted in which one –CH<sub>2</sub>– may also be replaced by –O-, –S-, or –NR' where R' is H or alkyl of 2 to 20 carbon atoms;

d) R<sup>1</sup> is the moiety –NR<sup>a</sup>R<sup>b</sup> wherein R<sup>a</sup>R<sup>b</sup> are optionally taken together with the nitrogen to which each is attached;  
30 R<sup>2</sup> is selected from

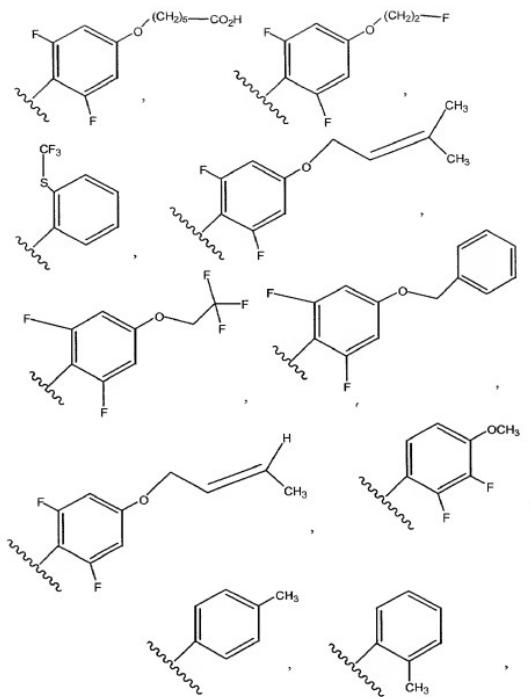


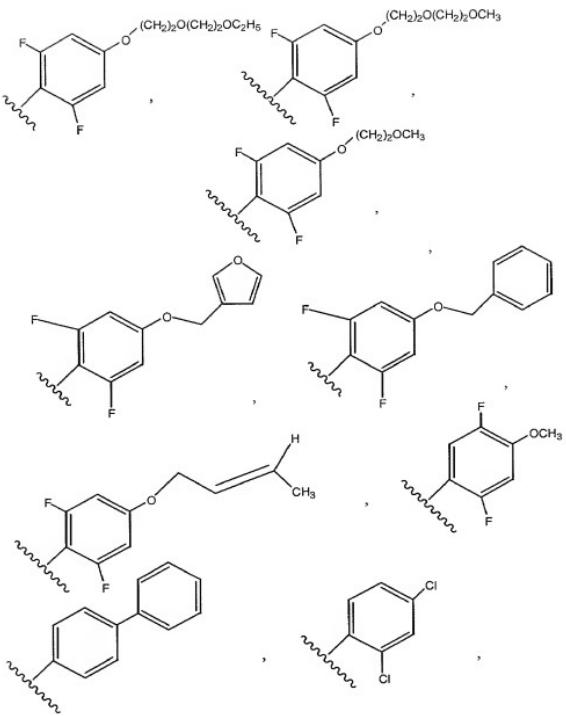


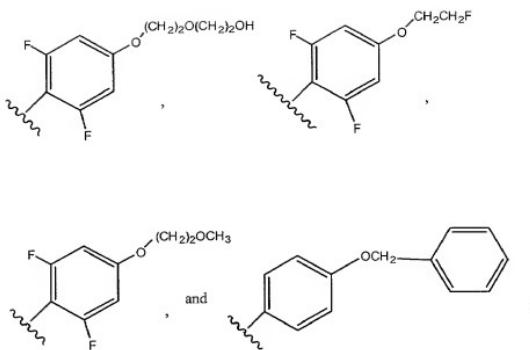




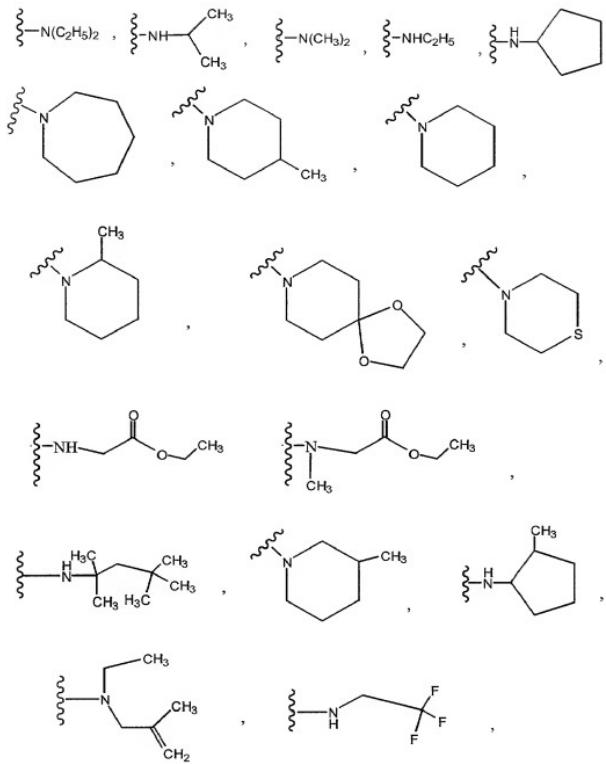
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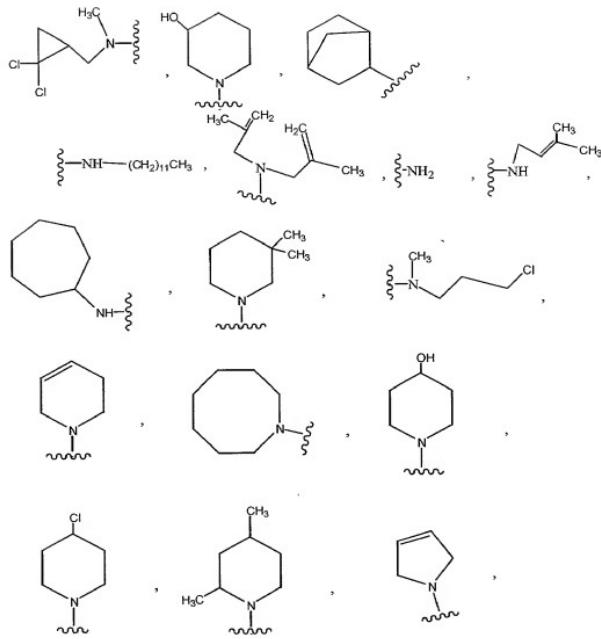


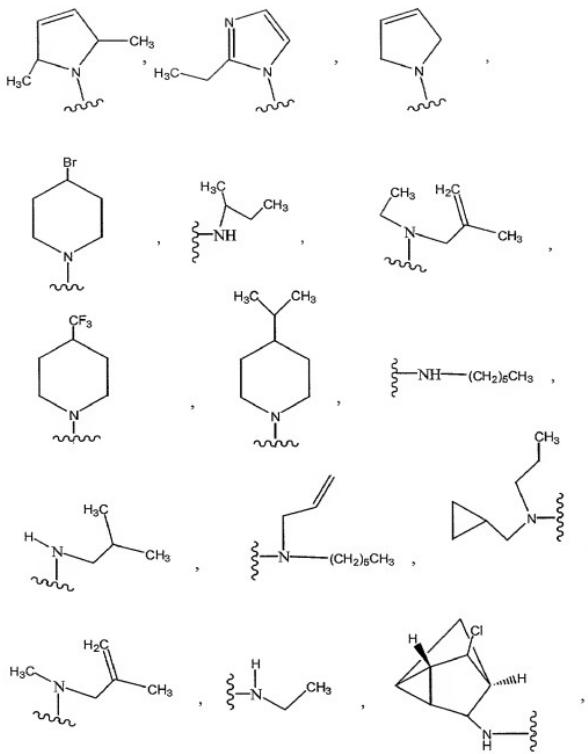


- 5     $\text{R}^3$  is halogen, alkoxy,  $-\text{NR}^c\text{R}^d$ , haloalkoxy of 1 to 12 carbon atoms, alkylthio of 1 to 12 carbon atoms, cyano, or  $-\text{N}_3$ ;  
       $\text{R}^4$  is H;  
e)  $\text{R}^1$  is the moiety  $-\text{NR}^a\text{R}^b$  wherein  $\text{R}^a\text{R}^b$  are optionally taken together with the nitrogen to which each is attached and wherein  $\text{R}^1$  is selected from

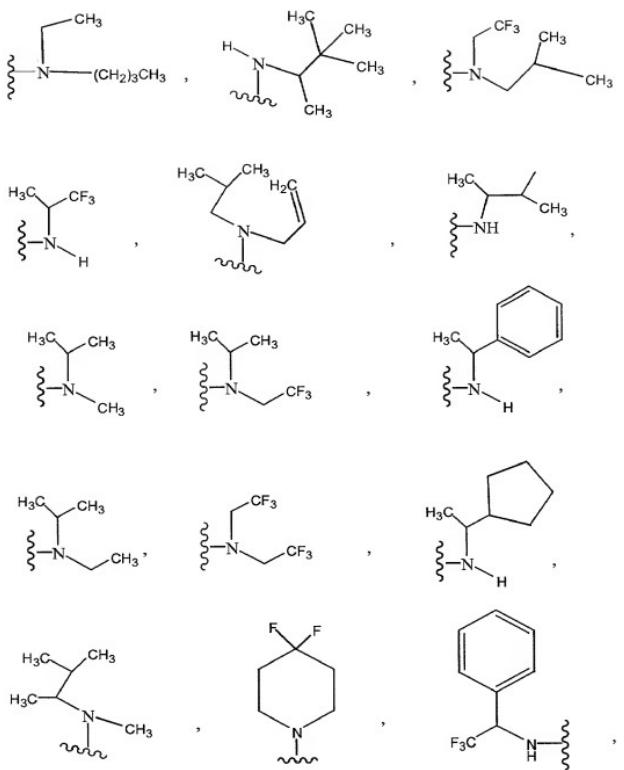


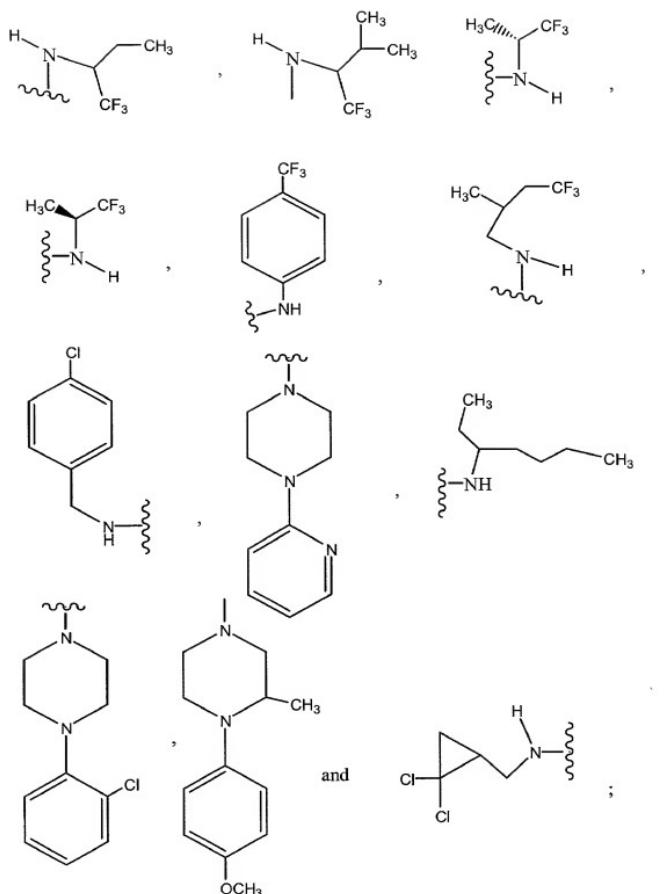
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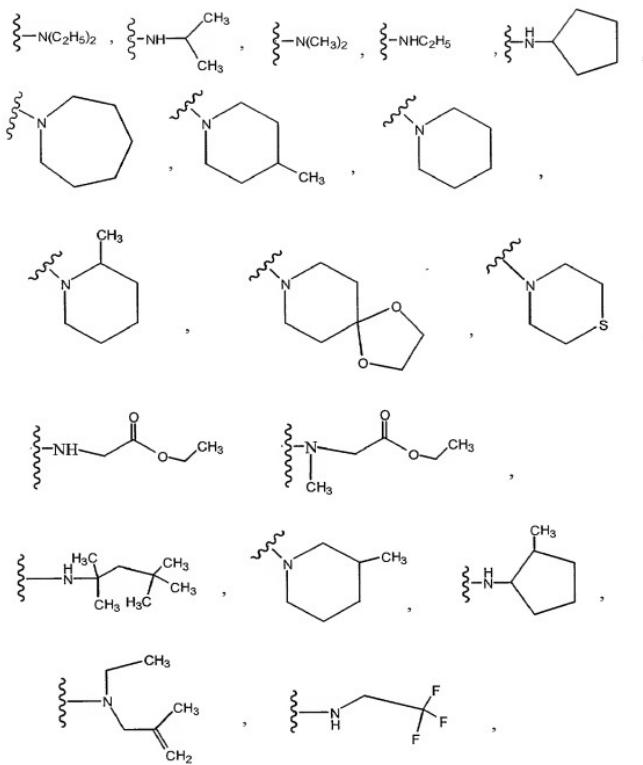
R<sup>2</sup> is optionally substituted phenyl;

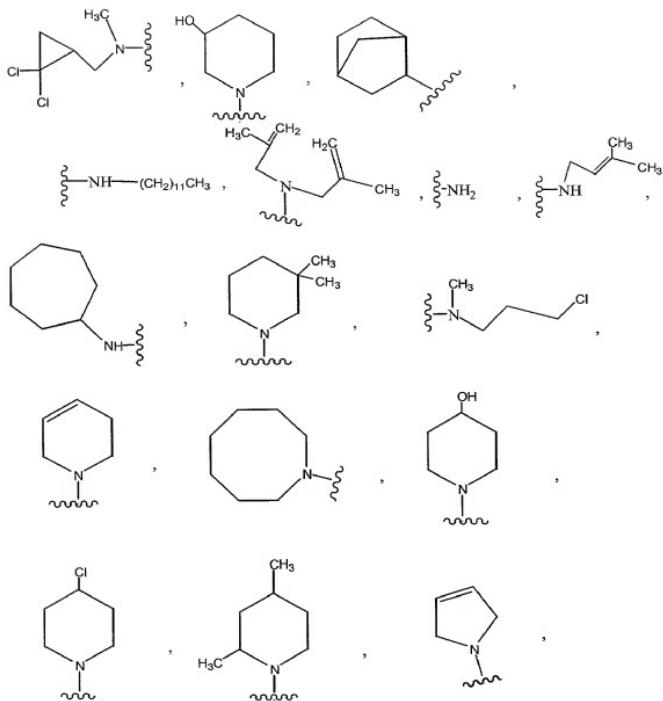
R<sup>3</sup> is halogen, alkoxy of 1 to 12 carbon atoms, -NR<sup>c</sup>R<sup>d</sup>, haloalkoxy of 1 to 12 carbon atoms, alkylthio of 1 to 12 carbon atoms, cyano, or -N<sub>3</sub>;

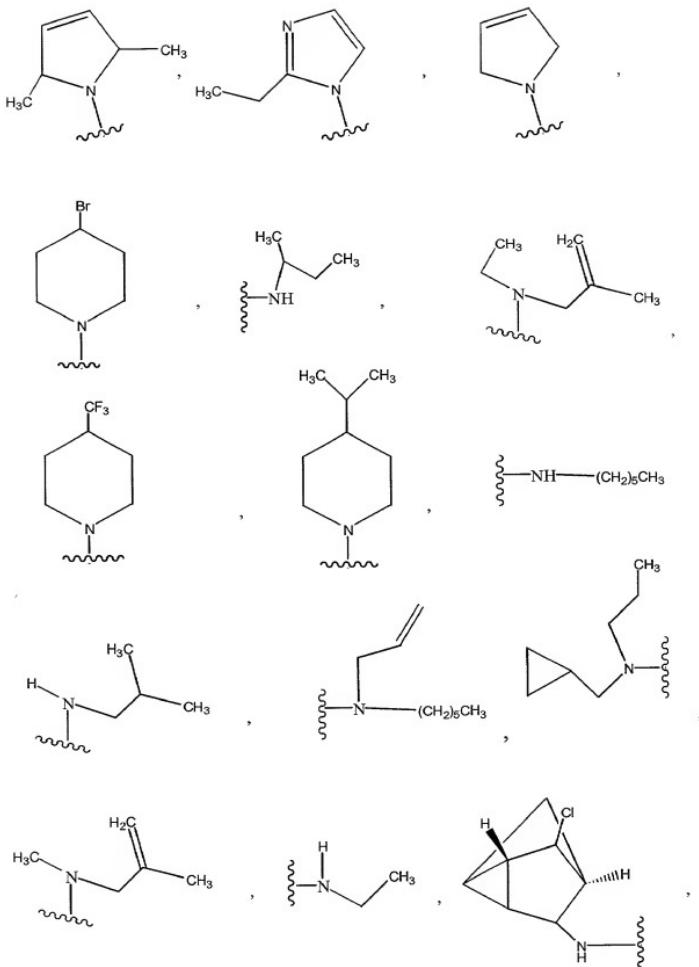
R<sup>4</sup> is H;

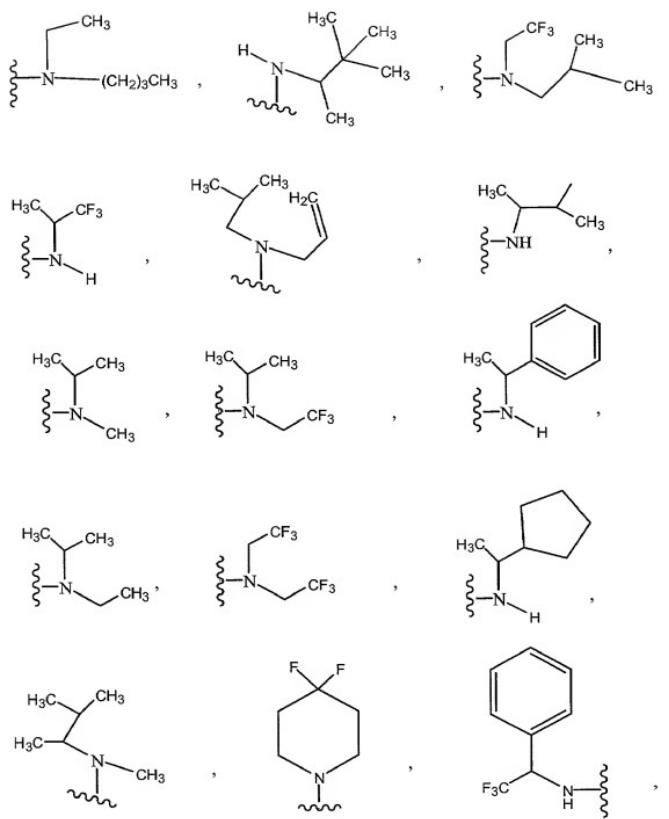
5

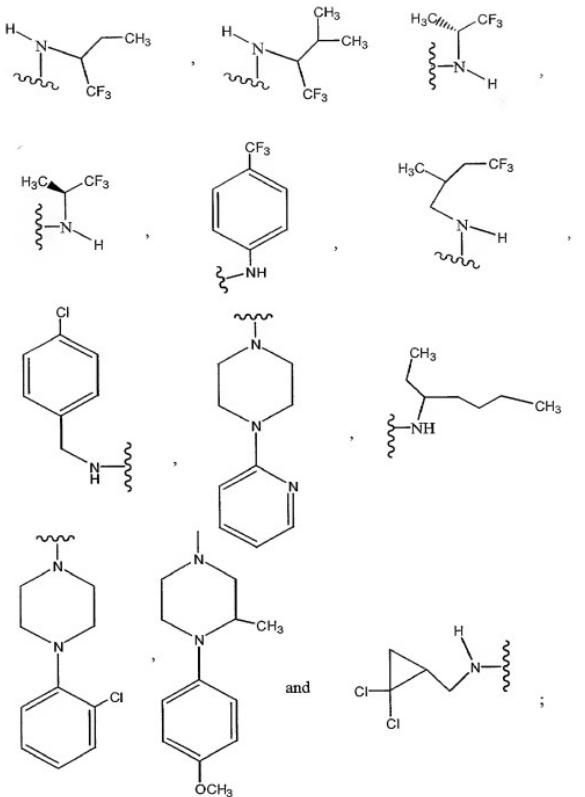
f) R<sup>1</sup> is the moiety -NR<sup>a</sup>R<sup>b</sup> wherein R<sup>a</sup>R<sup>b</sup> are optionally taken together with the nitrogen to which each is attached and wherein R<sup>1</sup> is selected from











$R^2$  is optionally substituted thienyl;

$R^3$  is halogen, alkoxy of 1 to 12 carbon atoms,  $-NR^cR^d$ , haloalkoxy of 1 to 12

- 5 carbon atoms, alkylthio of 1 to 12 carbon atoms, cyano, or -N<sub>3</sub>;

R<sup>4</sup> is H;

Also, among the most particularly preferred compounds for the methods of this invention according to Formula (I) are the following

5 compounds or a pharmaceutically acceptable salt thereof:

7-(1-azepanyl)-5-chloro-6-phenyl[1,2,4]triazolo[1,5-a]pyrimidine;

5-chloro-6-(2,6-difluorophenyl)-7-(4-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine;

5-chloro-6-(4-methoxyphenyl)-7-(1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine;

5-chloro-6-(2-chloro-6-fluorophenyl)-7-(4-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine;

5-chloro-6-(2-chloro-6-fluorophenyl)-7-(2-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine;

5-chloro-6-(2-chloro-6-fluorophenyl)-7-(4-thiomorpholinyl)[1,2,4]triazolo[1,5-a]pyrimidine;

25 methyl [[5-chloro-6-(2-chloro-6-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-yl](methyl)amino]acetate;

5-chloro-6-(2-chloro-6-fluorophenyl)-N-(1,1,3,3-tetramethylbutyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;

30

- 106290-57-6
- 7-(1-azepanyl)-5-chloro-6-(4-methoxyphenyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 7-(1-azepanyl)-6-(4-bromophenyl)-5-chloro[1,2,4]triazolo[1,5-a]pyrimidine;
- 5    5-chloro-7-(1-piperidinyl)-6-[2-(trifluoromethyl)phenyl][1,2,4]triazolo[1,5-a]pyrimidine;
- 10    6-(4-tert-butylphenyl)-5-chloro-7-(4-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 15    5-chloro-6-(4-methoxyphenyl)-7-(4-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 20    5-chloro-6-(4-methoxyphenyl)-7-(3-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 25    6-(4-bromophenyl)-5-chloro-7-(3-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 30    5-chloro-6-(3,4-difluorophenyl)-7-(4-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 35    5-chloro-6-(2,6-dichlorophenyl)-7-(2-methyl-1-pyrrolidinyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 40    5-chloro-6-(2-chlorophenyl)-7-(2-methyl-1-pyrrolidinyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 45    7-(1-azepanyl)-5-chloro-6-(3-chloro-4-methoxyphenyl)[1,2,4]triazolo[1,5-a]pyrimidine;

- 5-chloro-6-(3-chloro-4-methoxyphenyl)-7-(4-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 5-chloro-6-(3-chloro-4-methoxyphenyl)-7-(2-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 6-(4-tert-butylphenyl)-5-chloro-7-(2-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 5-chloro-7-(2-methyl-1-piperidinyl)-6-[3-(trifluoromethyl)phenyl][1,2,4]triazolo[1,5-a]pyrimidine;
- Diethyl 2-[6-(2,6-difluorophenyl)-5-ethoxy[1,2,4]triazolo[1,5-a]pyrimidin-7-yl]malonate;
- 7-(azepanyl)-5-chloro-6-(2-chloro-6-nitrophenyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 5-chloro-6-(2-chloro-6-fluorophenyl)-N-ethyl-N-(2-methyl-2-propenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 5-chloro-6-(2-chloro-6-fluorophenyl)-N-(2,2,2-trifluoroethyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 5-chloro-6-(2-chloro-6-fluorophenyl)-N-[(2,2-dichlorocyclopropyl)methyl]-N-methyl[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 1-[5-chloro-6-(2-chloro-6-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-yl]-3-piperidinol;

- 106290-57-656860
- N-bicyclo[2.2.1]hept-2-yl-5-chloro-6-(3-chloro-4-methoxyphenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 5 5-chloro-6-(2,5-difluorophenyl)-N-dodecyl[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 5-chloro-7-(4-methyl-1-piperidinyl)-6-(2,3,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 10 N-[5-chloro-6-(2,3,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-yl]-N-isopropylamine;
- 5-chloro-N-ethyl-N-(2-methyl-2-propenyl)-6-(2,3,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 15 N-allyl-5-chloro-6-(2-chloro-6-fluorophenyl)-N-(2-methyl-2-propenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 5-chloro-6-(2-chloro-6-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 20 5-chloro-6-(3-chloro-4-methoxyphenyl)-N-cycloheptyl[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 5-chloro-6-(3-chloro-4-methoxyphenyl)-7-(3,3-dimethyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 25 5-chloro-N-(3-chloropropyl)-N-methyl-6-(2,3,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 7-(1-azocanyl)-5-chloro-6-(2,3,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine;

- 5-chloro-6-(2,6-difluorophenyl)-7-(3,6-dihydro-1(2H)-  
pyridinyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 7-(1-azocanyl)-5-chloro-6-(2,6-difluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 5  
5-methoxy-6-(2-chloro-6-fluorophenyl)-7-(4-methyl-1-  
piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 10 [5-chloro-6-(2-chloro-6-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-  
y]methanol;
- 15 1-[5-chloro-6-(2,6-difluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-y]-4-  
piperidinol;
- 20 5-chloro-7-(4-chloro-1-piperidinyl)-6-(2,6-difluorophenyl)[1,2,4]triazolo[1,5-  
a]pyrimidine;
- 5-chloro-7-(4-thiomorpholinyl)-6-(2,3,6-trifluorophenyl)[1,2,4]triazolo[1,5-  
a]pyrimidine;
- 25 5-chloro-6-(2,6-difluorophenyl)-7-(2,4-dimethyl-1-  
piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 7-(4-methyl-1-piperidinyl)-5-amino-6-(2-chloro-6-  
25 fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 5-chloro-6-(2,6-difluorophenyl)-7-(2,5-dihydro-1H-pyrrol-1-  
yl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 30 5-chloro-6-(2-chloro-6-fluorophenyl)-7-(2,5-dimethyl-2,5-dihydro-1H-pyrrol-1-  
yl)[1,2,4]triazolo[1,5-a]pyrimidine;

- 5-chloro-6-(2-chloro-6-fluorophenyl)-7-(2-ethyl-1H-imidazol-1-yl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 5 7-(4-bromo-1-piperidinyl)-5-chloro-6-(2-chloro-6-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 10 5-chloro-6-(2-methylphenyl)-7-(4-thiomorpholinyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 15 6-(2-bromophenyl)-N-(sec-butyl)-5-chloro[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 5-chloro-N-ethyl-6-(4-methoxyphenyl)-N-(2-methyl-2-propenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 15 5-chloro-6-(4-methoxyphenyl)-7-(4-thiomorpholinyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 20 5-chloro-7-(4-chloro-1-piperidinyl)-6-[2-(trifluoromethyl)phenyl][1,2,4]triazolo[1,5-a]pyrimidine;
- 5-chloro-6-(2-chloro-6-fluorophenyl)-7-[4-(trifluoromethyl)-1-piperidinyl][1,2,4]triazolo[1,5-a]pyrimidine;
- 25 7-(4-bromo-1-piperidinyl)-5-chloro-6-(2,6-difluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 7-(4-bromo-1-piperidinyl)-5-chloro-6-(2-chlorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine;

5-chloro-N-ethyl-N-(2-methyl-2-propenyl)-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;

5-chloro-N-isopropyl-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;

5-chloro-7-(4-thiomorpholinyl)-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine;

10 7-(1-azepanyl)-5-chloro-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine;

5-chloro-6-(2-chloro-6-fluorophenyl)-7-[2-(1-pyrrolidinyl)-1-cyclopenten-1-yl][1,2,4]triazolo[1,5-a]pyrimidine;

15 5-chloro-7-(4-isopropyl-1-piperidinyl)-6-(4-methoxyphenyl)[1,2,4]triazolo[1,5-a]pyrimidine;

20 5-chloro-7-(2,4-dimethyl-1-piperidinyl)-6-(4-methoxyphenyl)[1,2,4]triazolo[1,5-a]pyrimidine;

5-chloro-7-[ethyl(2-methyl-2-propenyl)amino]-6-{4-nitrophenyl}[1,2,4]triazolo[1,5-a]pyrimidine;

25 7-(1-azepanyl)-5-chloro-6-{4-nitrophenyl}[1,2,4]triazolo[1,5-a]pyrimidine;

N-bicyclo[2.2.1]hept-2-yl-5-chloro-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;

30 5-chloro-6-(2,6-difluorophenyl)-N-(2,2,2-trifluoroethyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;

- 5-chloro-6-(2-chlorophenyl)-N-(2,2,2-trifluoroethyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 5 5-chloro-6-(2-chloro-6-fluorobenzyl)-7-tetrahydro-2-furanyl[1,2,4]triazolo[1,5-a]pyrimidine;
- 10 7-(allylsulfanyl)-5-chloro-6-(2-chloro-6-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 15 5-chloro-N-ethyl-6-mesityl-N-(2-methyl-2-propenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 20 5-chloro-N-ethyl-6-(2-methoxyphenyl)-N-(2-methyl-2-propenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 25 5-chloro-6-(2-chloro-6-fluorophenyl)-N-hexyl[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 30 5-chloro-7-(4-methyl-1-piperidinyl)-6-[4-(methylsulfanyl)phenyl][1,2,4]triazolo[1,5-a]pyrimidine;
- 35 5-chloro-N-ethyl-N-(2-methyl-2-propenyl)-6-[4-(methylsulfanyl)phenyl][1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 40 N-(sec-butyl)-5-chloro-6-[4-(methylsulfanyl)phenyl][1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 45 5-chloro-6-[4-(methylsulfanyl)phenyl]-7-(4-thiomorpholinyl)[1,2,4]triazolo[1,5-a]pyrimidine;

- 5-chloro-6-[2,6-dichloro-4-(trifluoromethyl)phenyl]-7-(4-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 7-(1-azepanyl)-5-chloro-6-[2,6-dichloro-4-(trifluoromethyl)phenyl][1,2,4]triazolo[1,5-a]pyrimidine;
- 5-chloro-6-(2-chloro-6-fluorophenyl)-7-[(2,2,2-trifluoroethyl)sulfanyl][1,2,4]triazolo[1,5-a]pyrimidine;
- 5-chloro-6-(2-chloro-6-fluorophenyl)-7-(4,4-dimethyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 5-chloro-6-[2,6-dichloro-4-(trifluoromethyl)phenyl]-N-ethyl-N-(2-methyl-2-propenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 5-chloro-6-[2,6-dichloro-4-(trifluoromethyl)phenyl]-7-(4-thiomorpholinyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 5-chloro-6-(3,5-difluorophenyl)-7-(4-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 5-chloro-6-(2-chloro-6-fluorophenyl)-7-(isopropylsulfanyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 5-chloro-6-(2-chloro-6-fluorophenyl)-7-tetrahydro-2-furanyl[1,2,4]triazolo[1,5-a]pyrimidine;
- 4-[5-chloro-7-(4-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidin-6-yl]aniline;
- N-{4-[5-chloro-7-(4-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidin-6-yl]phenyl}acetamide;

[5-chloro-6-(2-chloro-6-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-yl]methyl acetate;

- 5    5-chloro-6-(2-chloro-6-fluorophenyl)-7-(chloromethyl)[1,2,4]triazolo[1,5-a]pyrimidine;

diethyl 2-[6-(2-chloro-6-fluorophenyl)-7-(4-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidin-5-yl]malonate;

- 10    7-(1-azepanylmethyl)-5-chloro-6-(2-chloro-6-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine;

- 15    N-allyl-5-chloro-6-(2-chloro-6-fluorophenyl)-N-hexyl[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;

5-chloro-7-(4-methyl-1-piperidinyl)-6-[4-(trifluoromethoxy)phenyl][1,2,4]triazolo[1,5-a]pyrimidine;

- 20    5-chloro-7-(4-methyl-1-piperidinyl)-6-(4-phenoxyphenyl)[1,2,4]triazolo[1,5-a]pyrimidine;

5-chloro-6-(2-chloro-6-fluorophenyl)-N-(cyclopropylmethyl)-N-propyl[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;

- 25    5-chloro-7-(2-methyl-1-piperidinyl)-6-(4-phenoxyphenyl)[1,2,4]triazolo[1,5-a]pyrimidine;

- 30    5-chloro-6-(2-chloro-4-nitrophenyl)-7-(4-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine;

- 106290-57656860
- 5-chloro-6-(4-chloro-2,3,5,6-tetrafluorophenyl)-N-cyclopentyl[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 4-[5-chloro-2-methyl-7-(4-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidin-6-yl]-N,N-dimethylaniline;
- 6-(2-chloro-6-fluorophenyl)-5-methyl-7-(4-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 10 5-chloro-6-(2-chloro-6-fluorophenyl)-7-[2-(1-pyrrolidinyl)-1-cyclohexen-1-yl][1,2,4]triazolo[1,5-a]pyrimidine;
- 5-chloro-6-(2-chloro-6-fluorophenyl)-7-(methoxymethyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 15 5-chloro-6-{2-chloro-4-nitrophenyl}-7-[ethyl(2-methyl-2-propenyl)amino][1,2,4]triazolo[1,5-a]pyrimidine;
- 5-bromo-6-(2-chloro-6-fluorophenyl)-7-(isopropylsulfanyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 20 5-chloro-N-cyclopentyl-6-(4-ethoxy-2,3,5,6-tetrafluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 5-chloro-N-methyl-N-(2-methyl-2-propenyl)-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 25 4-bromo-1-[5-chloro-6-(2-chloro-6-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-yl]butyl acetate;

diethyl 2-allyl-2-[[5-chloro-6-(2-chloro-6-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-yl]oxy}malonate;

5 6-(2-chloro-6-fluorophenyl)-N-ethyl-5-methyl[1,2,4]triazolo[1,5-a]pyrimidin- 7-  
amine;

N-butyl-5-chloro-N-ethyl-6-(2,3,4,5,6-pentafluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;

10 6-(2-chloro-6-fluorophenyl)-5-(difluoromethoxy)-7-(4-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine;

5-chloro-6-(2-chloro-6-fluorophenyl)-7-[(4-chlorophenyl)sulfanyl][1,2,4]triazolo[1,5-a]pyrimidine;

15 5-chloro-6-(2-chloro-6-fluorophenyl)-7-[(2-methoxyphenyl)sulfanyl][1,2,4]triazolo[1,5-a]pyrimidine;

20 5-chloro-6-(2-chloro-6-fluorophenyl)-N-(1,2,2-trimethylpropyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;

5-chloro-6-(2,3,4,5,6-pentafluorophenyl)-N-(1,2,2-trimethylpropyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;

25 5-chloro-6-(2,4,6-trifluorophenyl)-N-(1,2,2-trimethylpropyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;

5-chloro-6-(4-fluorophenyl)-N-(1,2,2- trimethylpropyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;

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- 5,7-bis(4-methyl-1-piperidinyl)-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 5-chloro-6-(2-methylphenyl)-N-(1,2,2-trimethylpropyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 5-chloro-6-(2,4,5-trifluorophenyl)-N-(1,2,2-trimethylpropyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 10 6-(2-bromophenyl)-5-chloro-N-(1,2,2-trimethylpropyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 5-chloro-N-isobutyl-N-(2,2,2-trifluoroethyl)-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 15 5-chloro-N-isobutyl-6-(2-methylphenyl)-N-(2,2,2-trifluoroethyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 5-chloro-6-(2-chloro-6-fluorophenyl)-N-(2,2,2-trifluoro-1-methylethyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 20 5-chloro-6-(2,6-difluorophenyl)-N-(2,2,2-trifluoro-1-methylethyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 5-chloro-6-(2,2,2-trifluoro-1-methylethyl)-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 25 N-allyl-5-chloro-N-isobutyl-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;

- Y06290-52656860
- 5-chloro-N-(1,2-dimethylpropyl)-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 5-chloro-N-isopropyl-N-methyl-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 5-chloro-N-isopropyl-N-(2,2,2-trifluoroethyl)-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 7-butyl-5-chloro-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 5-chloro-N-(1-phenylethyl)-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 5-chloro-6-(2-chlorophenyl)-N-(2,2,2-trifluoro-1-methylethyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 5-chloro-N-ethyl-N-isobutyl-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 5-chloro-6-(2-chloro-6-fluorophenyl)-7-hexyl[1,2,4]triazolo[1,5-a]pyrimidine;
- 5-chloro-6-(2-methylphenyl)-N,N-bis(2,2,2-trifluoroethyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 5-chloro-N-cyclopentyl-N-methyl-6-(2,3,4,5,6-pentafluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 7-butyl-5-chloro-6-(2,6-difluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine;

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5-chloro-N-(1,2-dimethylpropyl)-N-methyl-6-(2,3,4,5,6-pentafluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;

5-chloro-6-(2-chloro-6-fluorophenyl)-7-phenyl[1,2,4]triazolo[1,5-a]pyrimidine;

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5-chloro-6-(2-chloro-6-fluorophenyl)-7-(2-methylpropanyl)[1,2,4]triazolo[1,5-a]pyrimidine;

5-chloro-6-(2-chloro-6-fluorophenyl)-7-pentyl[1,2,4]triazolo[1,5-a]pyrimidine;

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5-chloro-N-(1,2-dimethylpropyl)-N-methyl-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;

5-chloro-6-(2-chloro-6-fluorophenyl)-7-cyclohexyl[1,2,4]triazolo[1,5-

15 a]pyrimidine;

5-chloro-6-(2-bromo-5-chlorophenyl)-N-(2,2,2-trifluoro-1-methylethyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;

20 5-chloro-6-(2-chloro-6-fluorophenyl)-7-(3,3,3-trifluoropropyl)[1,2,4]triazolo[1,5-a]pyrimidine;

5-chloro-6-(2-chloro-6-fluorophenyl)-7-(3-methylphenyl)[1,2,4]triazolo[1,5-a]pyrimidine;

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[5-chloro-6-(2,4,6-trifluorophenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-7-yl]- (1-p-tolyl-ethyl)-amine;

5-chloro-6-(2,4,6-trifluoro-phenyl)-7-cyclohexyl[1,2,4]triazolo[1,5-a]pyrimidine;

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- 5-chloro-7-cyclohexyl-6-(2,3,4,5,6-pentafluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 5-chloro-6-(2-chloro-6-fluorophenyl)-7-(4,4-difluoro-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 7-(bicyclo[2.2.1]hept-2-ylamino)-5-chloro-6-[2-fluoro-4-nitrophenyl][1,2,4]triazolo[1,5-a]pyrimidine;
- 5-chloro-6-{2-fluoro-4-nitrophenyl}-7-(4-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- [5-chloro-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-yl] (2,2,2-trifluoro-1-phenylethyl)-amine;
- 5-chloro-N-[1-(trifluoromethyl)propyl]-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 5-bromo-6-(2-chloro-6-fluorophenyl)-7-cyclohexyl[1,2,4]triazolo[1,5-a]pyrimidine;
- 6-(2-chloro-6-fluorophenyl)-7-cyclohexyl[1,2,4]triazolo[1,5-a]pyrimidin-5-amine;
- [5-chloro-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-yl]-(2-methyl-1-trifluoromethyl-propyl)amine;

- 5-chloro-7-(3-cyclohexen-1-yl)-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 5-chloro-7-(1-cyclohexen-1-yl)-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 5-chloro-N-[(1R)-2,2,2-trifluoro-1-methylethyl]-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 10 5-chloro-N-[(1R)-2,2,2-trifluoro-1-methylethyl]-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 6-(2,4-difluorophenyl)-5-chloro-N-(2,2,2-trifluoro-1-methylethyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 15 5-chloro-6-(2,6-difluoro-4-methoxyphenyl)-7-(4-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 5-chloro-6-(2,6-difluoro-4-methoxyphenyl)-N-(2,2,2-trifluoro-1-methylethyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 20 5-chloro-7-cyclohexyl-6-(2,6-difluoro-4-methoxyphenyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 5-chloro-6-(2,6-difluoro-4-methoxyphenyl)-N-[(1S)-2,2,2-trifluoro-1-methylethyl][1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 25 7-cyclohexyl-6-(2,6-difluoro-4-methoxyphenyl)-5-methoxy[1,2,4]triazolo[1,5-a]pyrimidine;

- 5-chloro-7-(4-fluorocyclohexyl)-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 5-chloro-6-(2,6-dichloro-4-fluorophenyl)-7-(3,3,3-trifluoropropyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- N-(sec-butyl)-5-chloro-6-(2,6-dichloro-4-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 10 4-[5-chloro-7-[(2,2,2-trifluoro-1-methylethyl)amino][1,2,4]triazolo[1,5-a]pyrimidin-6-yl]-3,6-difluorophenol;
- 5-chloro-7-(3-cyclohexen-1-yl)-6-(2,6-difluoro-4-methoxyphenyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 15 5-chloro-6-(2,6-difluoro-4-methoxyphenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 5-chloro-N-cyclopentyl-6-(2,6-difluoro-4-methoxyphenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 20 5-chloro-6-(2,6-difluoro-4-methoxyphenyl)-7-(3,6-dihydro-1(2H)-pyridinyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 25 5-chloro-6-(2,6-difluoro-4-methoxyphenyl)-7-(4-thiomorpholinyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 7-(1-azepanyl)-5-chloro-6-(2,6-difluoro-4-methoxyphenyl)[1,2,4]triazolo[1,5-a]pyrimidine;

- 5-chloro-6-(2,6-difluoro-4-methoxyphenyl)-N-(1,2,2-trimethylpropyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 5-chloro-6-(2,6-difluoro-4-methoxyphenyl)-N-ethyl-N-(2-methyl-2-propenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 5-chloro-6-(2,6-difluoro-4-methoxyphenyl)-7-(4-fluorocyclohexyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 10 6-(4-{5-chloro-7-[(2,2,2-trifluoro-1-methylethyl)amino][1,2,4]triazolo[1,5-a]pyrimidin-6-yl]-3,5-difluorophenoxy)hexanoic acid;
- 2,6-difluoro-4-(2-fluoroethoxy)phenyl]-N-(2,2,2-trifluoro-1-methylethyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 15 5-chloro-N-isopropyl-6-[2-[(trifluoromethyl)sulfanyl]phenyl][1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 5-chloro-N-[4-(trifluoromethyl)phenyl]-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 20 5-chloro-N-(4,4,4-trifluoro-2-methylbutyl)-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 5-chloro-N-(4,4,4-trifluoro-2-methylbutyl)-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 25 5-chloro-6-(2,6-difluoro-4-methoxyphenyl)-7-(3-methyl-3-butenyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 5-chloro-6-(2,6-difluoro-4-methoxyphenyl)-7-isobutyl[1,2,4]triazolo[1,5-a]pyrimidine;

- 7-cyclopentyl-6-(2,6-difluoro-4-methoxyphenyl)-5-methoxy[1,2,4]triazolo[1,5-a]pyrimidine;
- 5      5-chloro-6-(2-thienyl)-N-[(1R)-2,2,2-trifluoro-1-methylethyl][1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 10     4-(5-chloro-7-(2,2,2-trifluoro-1-methyl-ethylamino)[1,2,4]triazolo[1,5-a]pyrimidin-6-yl]-3,5-difluoro-phenol;
- 15     {5-chloro-6-[2,6-difluoro-4-(2,2,2-trifluoro-ethoxy)-phenyl]}-[1,2,4]triazolo[1,5-a]pyrimidin-7-yl)-(2,2,2-trifluoro-1-methyl-ethyl)amine;
- 20     5-chloro-6-{2,6-difluoro-4-(methoxyphenyl)-N-(2,2,2-trifluoro-1-methylethyl)}-[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 25     (5-chloro-6-{4-[2-(2-ethoxyethoxy)-ethoxy]-2,6-difluoro-phenyl}[1,2,4]triazolo[1,5-a]pyrimidin-7-yl)-(2,2,2-trifluoro-1-methylethyl)amine;
- 30     (5-chloro-6-{2,6-difluoro-4-[2-(2-methoxy-ethoxy)ethoxy]-phenyl}-[1,2,4]triazolo[1,5-a]pyrimidin-7-yl)-(2,2,2-trifluoro-1-methylethyl)amine;
- 35     5-chloro-6-[2,6-difluoro-4-(3-furan-3-ylmethoxy)phenyl][1,2,4]triazolo[1,5-a]pyrimidin-7-yl)-N-(2,2,2-trifluoro-1-methylethyl)amine;
- 40     5-chloro-6-(2,5-difluoro-4-methoxyphenyl)-N-(1,2,2-trimethylpropyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 45     7-cyclohexyl-6-[2,6-difluoro-4-(2-methoxyethoxy)phenyl]-5-methoxy[1,2,4]triazolo[1,5-a]pyrimidine;

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- 5-chloro-6-(2-fluoro-4-methoxy-6-chlorophenyl)-N-(2,2,2-trifluoro-1-methylethyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 5-chloro-6-[2,6-difluoro-4-(2-fluoroethoxy)phenyl]-N-ethyl-N-(2-methyl-2-propenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 2-[2-(4-{5-chloro-7-[(2,2,2-trifluoro-1-methylethyl)amino][1,2,4]triazolo[1,5-a]pyrimidin-6-yl}-3,5-difluorophenoxy)ethoxy]ethanol;
- 5-chloro-6-(2,3-difluoro-4-methoxyphenyl)-N-(2,2,2-trifluoro-1-methylethyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 5-chloro-6-{4-(2-fluoroethoxy)-2,6-difluorophenyl}-N-(2,2,2-trifluoro-1-methylethyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 5-chloro-N-(4-chlorobenzyl)-6-(2-chloro-6-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 5-chloro-6-(2-chloro-6-fluorophenyl)-7-[4-(2-pyridinyl)-1-piperazinyl][1,2,4]triazolo[1,5-a]pyrimidine;
- 5-chloro-6-(2-chloro-6-fluorophenyl)-N-(1-ethylpentyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 5-chloro-6-(2-chloro-6-fluorophenyl)-7-[4-(2-chlorophenyl)-1-piperazinyl][1,2,4]triazolo[1,5-a]pyrimidine;
- 5-chloro-6-(2-chloro-6-fluorophenyl)-7-[4-(4-methoxyphenyl)-3-methyl-1-piperazinyl][1,2,4]triazolo[1,5-a]pyrimidine;

- 5-chloro-N-cyclopentyl-6-(2-chloro-6-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 5-chloro-7-phenoxy-6-(4-methoxy-phenyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 5-chloro-N-cyclopentyl-6-(4-methylphenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 5,7-diphenoxy-6-(4-methoxyphenyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 5-chloro-N-cyclopentyl-6-(2-chlorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 5-chloro-N,N-diethyl-6-[4-methoxyphenyl][1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- N-bicyclo[2.2.1]hept-2-yl-5-chloro-6-(2,4-dichlorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 5-chloro-6-(2-chloro-6-fluorophenyl)-7-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 5-cyano-7-(4-methyl-1-piperidinyl)-6-(2-chloro-5-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 5-(methylsulfanyl)-7-(4-methyl-1-piperidinyl)-6-(2-chloro-6-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine;

5-(methylsulfanyl)-7-(4-methyl-1-piperidinyl)-6-(2-chloro-5-(methylsulfanyl)phenyl)[1,2,4]triazolo[1,5-a]pyrimidine;

5-chloro-7-(1,4-dioxa-8-azaspiro[4,5]dec-8-yl)-6-(4-methoxyphenyl)[1,2,4]triazolo[1,5-a]pyrimidine;

5-chloro-N-ethyl-N-(2-methyl-2-propenyl)-6-(4-methylsulfanyl)phenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;

10 2-methyl-6,7-di-(4-methoxyphenyl)[1,2,4]triazolo[1,5-a]pyrimidine;

2-methyl-6-phenyl-7-(4-chlorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine;

2-trifluoromethyl-6-phenyl-7-(4-methoxyphenyl)[1,2,4]triazolo[1,5-a]pyrimidine;

15 5,7-diphenoxy-6-(2-methylpropyl)[1,2,4]triazolo[1,5-a]pyrimidine;

5-chloro-6-(3,4-difluorophenyl)-N-(isopropyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;

20 5-bromo-6-(4-bromophenyl)-7-dimethylamino[1,2,4]triazolo[1,5-a]pyrimidine;

5-bromo-6-(4-trifluoromethylphenyl)-7-dimethylamino[1,2,4]triazolo[1,5-a]pyrimidine;

25 5-chloro-6-(3,4-difluorophenyl)-7-dimethylamino[1,2,4]triazolo[1,5-a]pyrimidine;

30 5-chloro-6-(4-trifluoromethylphenyl)-N-(ethyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;

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- 7-(1-azepanyl)-5-chloro-6-(4-tert-butylphenyl)[1,2,4]triazolo[1,5-a]pyrimidine;  
ethyl {[5-chloro-6-(2-chloro-6-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-  
y]amino}acetate;
- 5 diethyl 5-chloro-6-(2,6-difluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-  
malonate;
- 10 5-chloro-6-(2,5-difluorophenyl)-N-(3-methyl-2-butenyl)[1,2,4]triazolo[1,5-  
a]pyrimidin-7-amine;
- 15 [5-chloro-6-(2-chloro-6-fluorophenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-7-yl]acetic  
acid methyl ester;
- 20 5-chloro-6-(2,6-difluorophenyl)-7-(2-ethyl-1H-imidazol-1-yl)[1,2,4]triazolo[1,5-  
a]pyrimidine;  
5-chloro-N,N-diethyl-6-[4-(methylsulfanyl)phenyl][1,2,4]triazolo[1,5-  
a]pyrimidin-7-amine;
- 25 ethyl [6-(2-chloro-6-fluorophenyl)-7-(4-methyl-1-piperidinyl)- [1,2,4]triazolo[1,5-  
a]pyrimidin-5-yl]acetate;
- 30 5-chloro-N-ethyl-N-(2-methyl-2-propenyl)-6-(4-  
phenoxyphenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;  
dimethyl 2-[5-chloro-6-(2-chloro-6-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-  
7-yl]malonate;
- 35 diethyl 2-{{5-chloro-6-(2-chloro-6-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-  
y]oxy}-2-isobutylmalonate;

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- 2-[5-chloro-6-(2-chloro-6-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-yl]-1,3-cyclohexanedione;
- 2-[5-chloro-6-(2-chloro-6-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-yl]cyclohexanone;
- 5-chloro-7-(3-nitro-4-methylanilino)-6-(2, 4, 6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 10 7-cyclohexyl-6-[2,6-difluoro-4-(2-methoxyethoxy)phenyl]5-(2-methoxyethoxy)[1,2,4]triazolo[1,5-a]pyrimidine;
- 15 7-(3-bromophenyl)-2-ethyl-6-(4-methoxyphenyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 7-(3-bromophenyl)-6-(3-chlorophenyl)-2-ethyl[1,2,4]triazolo[1,5-a]pyrimidine;
- 20 7-(4-bromophenyl)-2-ethyl-6-[4-(trifluoromethyl)phenyl][1,2,4]triazolo[1,5-a]pyrimidine;
- 5-chloro-6-(2-chloro-6-fluorophenyl)-N-(3,4,5-trimethoxybenzyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 25 7-(2-benzyl-4,5-dihydro-1H-imidazol-1-yl)-5-chloro-6-(2-chloro-6-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- N-4-[5-chloro-6-(2-chloro-6-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-yl-N,N-1-diethyl-1,4-pentanediamine;
- 30 5-chloro-N-(3-methyl-2-butenyl)-6-phenyl[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;

- 5-dimethylamino-6-phenyl-N-cyclopentyl[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 5 5-chloro-7-[(2-furylmethyl)sulfanyl]-6-(4-methoxyphenyl)[1,2,4]triazolo[1,5-a]pyrimidine;
- 6-[1,1'-biphenyl]-4-yl-5-chloro-N-cyclopentyl[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 10 6-[4-(benzyloxy)phenyl]-5-chloro-N-isopropyl[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 15 5-chloro-N-[(2,2-dichlorocyclopropyl)methyl]-6-(3,4,5-trimethoxyphenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- N-cyclopentyl-6-(2-fluorophenyl)-5-hydrazino[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 20 5-chloro-N-ethyl-6-(2-methylphenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 6-(4-tert-butylphenyl)-5-chloro-N-isopropyl[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 25 5-chloro-6-[2,6-difluoro-4-[(3-methyl-2-butenyl)oxy]phenyl]-N-(2,2,2-trifluoro-1-methylethyl)-I-[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;
- 5-chloro-6-[2,6-difluoro-4-(1-propenyloxy)phenyl]-N-(2,2,2-trifluoro-1-methylethyl)-I-[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;

30

5-chloro-N-(3-tricyclo[2.2.1.0<sup>2,6</sup>]hept-1-yl)-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine;

- 5  
5-azido-7-cyclohexyl-6-(2-fluoro-6-chlorophenyl) [1,2,4]triazolo[1,5-a]pyrimidine;

5-azido-6-[2-chloro-6-fluorophenyl]-7-(4-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine;

- 10 2,5-dichloro-7-(4-methyl-1-piperidinyl)-6-[2-chloro-6-fluorophenyl][1,2,4]triazolo[1,5-a]pyrimidine.

It is understood that the definition of compounds of Formula (I), when R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>a</sup>, R<sup>b</sup>, R<sup>c</sup>, R<sup>d</sup>, or R' contain asymmetric carbons, encompass 15 all possible stereoisomers and mixtures thereof which possess the activity discussed below. In particular, the definition encompasses racemic modifications and any optical isomers, (R) and (S), which possess the indicated activity. Optical isomers may be obtained in pure form by standard separation techniques or enantiomer specific synthesis. It is understood that 20 this invention encompasses all crystalline forms of compounds of Formula (I). The pharmaceutically acceptable salts of the basic compounds of this invention are those derived from such organic and inorganic acids as: lactic, citric, acetic, tartaric, fumaric, succinic, maleic, malonic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, methanesulfonic, and similarly known 25 acceptable acids. Where R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>a</sup>, R<sup>b</sup>, R<sup>c</sup>, R<sup>d</sup>, or R' contains a carboxyl group, salts of the compounds in this invention may be formed with bases such as alkali metals (Na, K, Li) or alkaline earth metals (Ca or Mg).

- For the compounds defined above and referred to herein, unless otherwise 30 noted, the following terms are defined.

The term halogen atom may denote a bromine, iodine, chlorine or fluorine atom, and is especially a bromine, chlorine or fluorine atom.

- The terms alkyl, alkenyl, alkynyl, alkadienyl as used herein with respect to a radical or moiety refer to a straight or branched chain radical or moiety. As a rule, such radicals have up to 12, in particular up to 6 carbon atoms. Suitably an alkyl moiety has from 1 to 6 carbon atoms, preferably from 1 to 3 carbon atoms. A preferred alkyl moiety is an ethyl or especially a methyl group.
- Suitably an alkenyl moiety has from 2 to 12 carbon atoms. A preferred alkenyl moiety has from 2 to 6 carbon atoms. Most preferred is allyl or especially a 2-methylallyl group. Any of the alkyl, alkenyl, alkynyl, alkadienyl groups as used herein with respect to the radical or moiety may optionally be substituted with one or more of substituents which include for example, halogen atoms, nitro, cyano, thiocyanato, cyanato, hydroxyl, alkyl, haloalkyl, alkoxy, haloalkoxy, amino, alkylamino, dialkylamino, formyl, aryl, alkoxy carbonyl, carboxyl, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, carbamoyl, alkylamido, phenyl, phenoxy, benzyl, benzyloxy, heterocyclyl, especially furyl, and cycloalkyl, especially cyclopropyl, groups. Typically, 0-3 substituents may be present.
- Cycloalkyl or cycloalkenyl as used herein with respect to a radical or moiety refer to a cycloalkyl or cycloalkenyl group having 3 to 8 carbon atoms preferably 3 to 6 carbon atoms or a cycloalkenyl group having 5 to 8 carbon atoms, preferably 5 to 7 carbon atoms, in particular cyclopentyl, cyclohexyl or cyclohexenyl being optionally substituted by one or more of substituents which include for example, halogen atoms, nitro, cyano, thiocyanato, cyanato, hydroxyl, alkyl, haloalkyl, alkoxy, haloalkoxy, amino, alkylamino, dialkylamino, formyl, alkoxy carbonyl, carboxyl, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, carbamoyl, alkylamido, phenyl, phenoxy, benzyl, benzyloxy, heterocyclyl, especially furyl, and cycloalkyl, especially cyclopropyl, groups. Typically, 0-3 substituents may be present. Optionally, -CH<sub>2</sub>- group of the

cycloalkyl or cycloalkenyl radical or moiety may optionally be replaced with -O-, -S- or -NR' where R' is H or an alkyl group of 2 to 12 carbon atoms.

A bicycloalkyl group may contain from 5 to 10 carbon atoms.

5

Aryl as used herein with respect to the radical or moiety refers to an aryl group having 6, 10 or 14 carbon atoms, preferably 6 to 10 carbon atoms, in particular, phenyl, or naphthyl group being optionally substituted by one or more independently selected substituents which include, halogen atoms, nitro, cyano, alkenyl, thiocyanato, cyanato, hydroxyl, alkyl, haloalkyl, alkoxy, alkenyloxy, haloalkoxy, amino, alkylamino, dialkylamino, formyl, alkoxy carbonyl, carboxyl, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, carbamoyl, alkylamido, phenyl, phenoxy, benzyl, benzyloxy, heterocycl, and cycloalkyl, groups. Typically, 0-5 substituents may be present.

15

Aralkyl as used herein means an aryl-alkyl group in which the aryl and alkyl group are previously defined. Exemplary aralkyl groups include benzyl and phenethyl.

20 Aralkyloxy as used herein refers to an aryl-alkyl-O- group in which the alkyl group and aryl group are previously described.

Phenyl as used herein refers to a 6-membered aromatic ring.

25 Heterocycl group may be a single ring, a bicyclic ring system or a system of annelated or spiro-fused rings as a saturated or unsaturated moiety or radical having 3 to 12 ring atoms with 5 to 8 ring atoms preferred with 5 or 6 ring atoms more preferred selected from carbon, oxygen, sulfur and nitrogen, one or more, typically one or two, of which being oxygen, nitrogen or sulfur, being 30 optionally substituted by one or more of substituents which include for example, halogen atoms, preferably fluorine, nitro, cyano, thiocyanato,

- cyanato, hydroxyl, alkyl of 1 to 12 carbon atoms, preferably 1 to 6 carbon atoms, haloalkyl, preferably haloalkyl of 1 to 6 carbon atoms, alkoxy, alkoxy of 1 to 12 carbon atoms, preferably alkoxy of 1 to 6 carbon atoms, haloalkoxy, amino, alkylamino, dialkylamino, formyl, alkoxy carbonyl, carboxyl, alkanoyl,
- 5 alkylthio, alkylsulphinyl, alkylsulphonyl, carbamoyl, alkylamido, phenyl, phenoxy, benzyl, benzyloxy, heterocycl, especially furyl, and cycloalkyl, especially cyclopropyl, groups. Typically, 0-3 substituents may be present. Optionally substituted heterocycl groups include pyrrolodinyl, pyrazolidinyl, piperidinyl, piperazinyl or morpholin-4-yl, pyridinyl, 2,3-dehydropiperid-3-yl,
- 10 tetrahydropyranyl, tetrahydrofuranyl or tetrahydrothienyl, N-methyl-2,3-dehydropiperid-3-yl, pyrimidinyl, pyrrolidinyl, furyl, pyranyl, morpholinyl, tetrahydropyridine, thienyl, pyrrolidinyl, piperidyl, dihydropiperidyl, dihydropyridinyl, thiazanyl, morpholinyl, thiazinyl, azepanyl, azocanyl and dioxa-aza-spiro-decyl.
- 15 When any of the foregoing substituents are designated as being optionally substituted, the substituent groups which are optionally present may be any one or more of substituents which include for example, halogen atoms, nitro, cyano, thiocyanato, cyanato, hydroxyl, alkyl, haloalkyl, alkoxy, haloalkoxy,
- 20 amino, alkylamino, dialkylamino, formyl, alkoxy carbonyl, carboxyl, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, carbamoyl, alkylamido, phenyl, phenoxy, benzyl, benzyloxy, heterocycl, especially furyl, and cycloalkyl, especially cyclopropyl, groups. Typically, 0-3 substituents may be present. When any of the foregoing substituents represents or contains an alkyl
- 25 substituent group, this may be linear or branched and may contain up to 12, preferably up to 6, and especially up to 4, carbon atoms. When any of the foregoing substituents represents or contains an aryl or cycloalkyl moiety, the aryl or cycloalkyl moiety may itself be substituted by one or more halogen atoms, nitro, cyano, alkyl, haloalkyl, alkoxy or haloalkoxy groups. In the case
- 30 of cycloalkyl and heterocycl groups, optional substituents also include groups which together with two adjacent carbon atoms of the cycloalkyl or

heterocycl group form a saturated or unsaturated hydrocarbyl ring. In other words, a saturated or unsaturated hydrocarbyl ring may be optionally fused with the cycloalkyl or heterocycl group.

- 5 When any of the foregoing substituents represents or contains an aryl or cycloalkyl moiety, the aryl or cycloalkyl moiety may itself be substituted by one or more halogen atoms, nitro, cyano, alkyl, haloalkyl, alkoxy or haloalkoxy groups. In the case of cycloalkyl and heterocycl groups, optional substituents also include groups which together with two adjacent carbon
- 10 atoms of the cycloalkyl or heterocycl group form a saturated or unsaturated hydrocarbyl ring. In other words, a saturated or unsaturated hydrocarbyl ring may be optionally fused with the cycloalkyl or heterocycl group.

- 15 Optionally substituted moieties may be unsubstituted or have from one up to the maximal possible number of substituents. Typically, 0 to 3 substituents are present.

- 20 The present invention accordingly provides a pharmaceutical composition which comprises a compound of this invention in combination or association with a pharmaceutically acceptable carrier. In particular, the present invention provides a pharmaceutical composition which comprises an effective amount of a compound of this invention and a pharmaceutically acceptable carrier. As used in accordance with this invention, the term providing an effective amount of a compound means either directly administering such compound, or administering a prodrug derivative, or analog which will form an effective amount of the compound within the body.
- 25

#### DESCRIPTION OF THE INVENTION

- 30 Compounds of this invention are prepared according to the procedures described in U.S. Patent Nos. 5,593,996; 5,756,509; 5,948,783; 5,981,534;

5,612,345; 5,994,360; 6,020,338; 5,985,883; 5,854,252; 5,808,066;  
5,817,663; 5,955,252; 5,965,561; 5,986,135 ; and 5,750,766 which are  
hereby incorporated herein by reference.

- 5 Representative compounds of this invention were evaluated in several  
standard pharmacological test procedures that showed that the compounds  
of this invention possess significant activity as promoters of microtubule  
polymerization and are antineoplastic agents. Based on the activity shown in  
the standard pharmacological test procedures, the compounds of this  
10 invention are therefore useful as anticancer agents. Associated cancers are  
selected from the group consisting of breast, colon, lung, prostate,  
melanoma, epidermal, leukemia, kidney, bladder, mouth, larynx, esophagus,  
stomach, ovary, pancreas, liver, skin and brain. In particular the compounds  
of this invention possess an effect similar to Paclitaxel. The test procedures  
15 used and results obtained are shown below.

**CYTOTOXICITY STANDARD PHARMACOLOGICAL TEST PROCEDURE  
USING MTS AS DETECTION REAGENT**

This standard pharmacological test procedure identifies representative  
examples of substituted triazolopyrimidine compounds of the invention, which  
20 further includes compounds of Formula (I), which kill various human cancer  
cell lines. The test is based on the conversion by viable cells, but not by dead  
cells, of the tetrazolium salt, MTS, into a water-soluble colored formazan  
which is detected by spectrophotometry. The test procedure was used to  
identify the most potent compounds within a series of related structures which  
25 were known or suspected to have a microtubule mechanism of action. The  
most potent compounds were then taken forward into other test procedures  
which specifically analyzed effects on microtubules.

### Part 1. Cytotoxicity with HeLa Cells

In the first cytotoxicity test, representative compounds of the invention were tested with the HeLa human cervical carcinoma cell line at a single concentration. HeLa cells (ATCC CCL2.2) were routinely maintained by twice-weekly subculture in fresh medium. Medium was RPMI-1640 with L-glutamine, supplemented with 10% heat-inactivated fetal calf serum, 100 units/ml penicillin, and 100 µg/ml streptomycin.

For assay, HeLa cells were harvested by trypsinization, washed, counted and distributed to wells of 96-well flat-bottom microtiter plates at 1000 cells per well in 100 µl of medium. The plates were incubated at 37° in humidified 5% CO<sub>2</sub> in air for about 24 hr.

On day 2, compounds for test were diluted and added to wells. Compounds were dissolved in dimethyl sulfoxide (DMSO) at 10 mg/ml. These solutions were diluted into medium to give solutions of 20 µg/ml, and then 100 µl was added in duplicate to wells already containing cells, to give final drug concentrations of 10 µg/ml and a final DMSO concentration of 0.1%. Each plate also contained the following controls: cells with no drug (uninhibited cell growth = maximal MTS response = control response); cells plus 100 nM paclitaxel (all cells killed = minimal MTS response); and medium only (MTS reagent control). The plates were returned to the incubator for three days.

After three days of culture with test compounds (day 5 overall), the MTS assay was done on all wells of the plates. Twenty µl of the combined MTS/PMS reagent (Promega "CellTiter 96 Aqueous Non-Radioactive Cell Proliferation Assay," catalog no. G5421; see Technical Bulletin No. 169, Revised 9/96) were added to each well with a repeating pipettor, and the plates were returned to the 37° incubator for 2 hr before recording the absorbance of each well at 490 nm using an ELISA plate reader.

The absorbance values of the duplicate sample wells were averaged and expressed as a percentage of the average value of the control wells. Percentages less than 100 indicated that the test compounds had exerted a cytotoxic effect on the cells. The results of this pharmacological test procedure are displayed in Table 1.

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**Table 1**

Evaluation of Representative Compounds of the Invention in the  
MTS Cytotoxicity Standard Pharmacological Test Procedure with  
HeLa Cells

Ex No.	Percent of Control at 10 ug/ml
1	-1.6
2	10.4
4	2.9
5	-0.8
6	-0.4
7	0.6
8	2
9	8.1
12	0.3
19	-1.3
24	3.7
27	2.2
28	3.4
30	-0.4
32	20.3
33	-1.3
35	17.6
37	-1.6
38	0.2
39	10.6
41	7.1
42	-0.1

Table 1 (cont)

Ex No.	Percent of Control at 10 ug/ml
43	5.8
47	0
48	13.9
49	12
54	-0.1
59	0.9
60	4.9
61	-1.2
62	-0.7
63	10.6
64	-2
65	-0.6
66	-0.7
70	1.4
72	-1.8
73	15.6
79	7.1
82	-1.5
87	-0.2
99	1.8
102	1.1
103	-0.7
105	0
113	-0.3
116	-1.3
117	-0.1
121	-0.8

Table 1 (cont)	
Ex No.	Percent of Control at 10 ug/ml
122	2.1
123	-2.2
124	-1.6
127	-0.9
128	-0.3
130	5.4
132	3.4
133	10.7
135	-1.1
140	-0.9
141	10.8
143	92.8
144	2.3
145	16.2
146	16.1
149	7.8
150	3.4
151	9.6
157	-2.7
158	-0.4
159	-1
160	1.1
163	27.2
167	-2.5
168	8.7
169	23.8
170	22.6

Table 1 (cont)	
Ex No.	Percent of Control at 10 ug/ml
172	-0.9
173	-0.6
174	0.6
175	1.9
176	-0.6
177	8.5
180	-0.3
181	-1.5
182	-1.7
183	-0.1
184	1.3
185	1.5
186	1
187	-1.4
188	8.8
189	2.2
213	10.2
216	5.8
217	-0.5
225	-1

**Part 2. Cytotoxicity with COLO 205 Cells**

5 In the second cytotoxicity standard pharmacological test procedure, representative compounds of the invention were tested with the COLO 205 human colon adenocarcinoma cell line at six concentrations, in order to determine IC<sub>50</sub> values. COLO 205 cells (ATCC CCL 222) were routinely maintained by thrice-weekly subculture in fresh medium. Medium was RPMI-

1640 with L-glutamine, supplemented with 10% heat-inactivated fetal calf serum, 20 mM HEPES, 100 units/ml penicillin, and 100 µg/ml streptomycin.

For the test procedure, COLO 205 cells were harvested by trypsinization, washed, counted and distributed to wells of 96-well flat-bottom microtiter plates at 1000 cells per well in 100 µl of medium. In addition, one row of wells on an additional plate received cells as above ("time 0" plate). All plates were incubated at 37° in humidified 5% CO<sub>2</sub> in air for about 24 hr.

On day 2, compounds for test were diluted and added to wells. Compounds were dissolved in DMSO at 10 mg/ml. For each compound, six serial 3-fold dilutions were prepared in medium. The highest drug concentration with cells was 5 µg/ml and the highest DMSO concentration was 0.05%. Drugs were added in duplicate to wells in 100 µl volume. Each plate also contained the following controls: cells with no drug (uninhibited cell growth = maximal MTS response); cells plus 100 nM paclitaxel (all cells killed = minimal MTS response); and medium only (MTS reagent control). The plates were returned to the incubator for three days.

At the time of drug addition to the experimental plates, the MTS assay was run on the "time 0" plate. This produced the "time 0 MTS value" which was related to the number of viable cells per well at the time of drug addition. The MTS values of the wells of the experimental plates were lower than, higher than, or the same as the time 0 value, depending on whether a drug killed the cells, did not inhibit cell growth, or was cytostatic, respectively.

After three days of culture with test compounds (day 5 overall), the MTS assay was done on all wells of the experimental plates. The results for each plate were calculated separately, using its own controls. The absorbance values of the duplicate sample wells were averaged and divided by the average of the "time 0" values. The average of the control wells without drug, divided by the average "time 0" value, gave the maximal relative increase in MTS color yield due to cell growth during the final three days of culture. The average of the control wells with paclitaxel, divided by the "time 0"

value, gave the minimal relative color yield for cells that were completely killed. The six values for each compound were plotted against concentration, and the concentration that produced a relative color yield half way between the maximum and minimum was taken as the  $IC_{50}$  value. The most potent compounds had the lowest  $IC_{50}$  values. Test results of representative compounds of the invention are displayed in Table 2.

In addition, some compounds of the invention were tested in duplicate at 25 and 50 µg/ml with COLO 205 cells in the MTS cytotoxicity pharmacological test procedure. Results were expressed as a percent of the average value of the control wells. Percentages less than 100 indicated that the test compounds had exerted a cytotoxic effect on the cells. These test results are also displayed in Table 2.

Table 2

**Evaluation of Representative Compounds of the Invention in the MTS  
Cytotoxicity Standard Pharmacological Test Procedure with COLO 205**

5

Cells

Ex No.	IC50 ( $\mu$ g/ml)	n	% of Control At	
			25 $\mu$ g/ml	50 $\mu$ g/ml
1	0.84			
2	0.092			
3	0.82			
4	0.082			
5	0.057			
6	0.16			
7	0.12			
8	3.3			
9	0.86			
10	0.35			
11	2.5			
12	0.32	2		
13	4.3			
14	0.22			
15	1.2			
16	4.8			
17	0.91			
18	0.33			
19	0.25			
20	1			
21	2.8			
22	4.6			

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Table 2 (cont)

Ex No.	IC50 ( $\mu$ g/ml)	n	% of Control At	
			25 $\mu$ g/ml	50 $\mu$ g/ml
23	3.7			
24	>5			
25	>5 a			
26	0.33			
27	0.033			
28	0.08			
29	0.29			
30	0.31	2		
31	2.8			
32	>5			
33	0.062			
34	0.44			
35	0.026	3		
36	0.1			
37	>5			
38	2.5			
39	2.2			
40	0.31			
41	0.062			
42	0.33			
43	0.084			
44	0.64			
45	4.8			
46	0.31			
47	0.11			
48	0.13			

Table 2 (cont)

Ex No.	IC50 ( $\mu$ g/ml)	n	% of Control At	
			25 $\mu$ g/ml	50 $\mu$ g/ml
49	0.15			
50	2.1			
51	0.86			
52	0.7			
53	1.3			
54	0.094			
55	0.59			
56	0.86			
57	0.64			
58	1			
59	0.18			
60	0.19			
61	0.095			
62	0.13			
63	0.16			
64	0.68	2		
65	0.18			
66	0.11			
67	0.34			
68	1.7	2		
69	0.36			
70	0.22			
71	0.87	2		
72	0.22			
73	0.13			
74	0.31			

Table 2 (cont)

Ex No.	IC50 ( $\mu$ g/ml)	n	% of Control At	
			25 $\mu$ g/ml	50 $\mu$ g/ml
75	4.3			
76	0.37	2		
77	0.66	2		
78	2.4			
79	0.27			
80	2.6	2		
81	2.5	2		
82	0.038			
83	3	2		
84	2.8			
85	2.8	2		
86	0.26	2		
87	0.24			
88	2.8	2		
89	2.9	2		
90	1			
91	0.39	2		
92	1.8			
93	2.7	2		
94	3.5	2		
95	3.8			
96	0.79	2		
97	>5 a			
98	2	2		
99	0.064			
100	>5 a			

Ex No.	IC50 ( $\mu\text{g/ml}$ )	n	% of Control At	
			25 $\mu\text{g/ml}$	50 $\mu\text{g/ml}$
101	4.4			
102	2.3			
103	0.27			
104	0.25	2		
105	0.12	2		
106	>5 a			
107	0.11	2		
108	0.63	2		
109	3.5			
110	0.32	2		
111	0.39	2		
112	0.34			
113	0.91			
114	3.7			
115	>5 a			
116	>5			
117	0.26			
118	1.2	2		
119	0.75	2		
120	1.4	2		
121	2.7			
122	0.73			
123	>5			

Ex No.	IC50 ( $\mu$ g/ml)	n	% of Control At	
			25 $\mu$ g/ml	50 $\mu$ g/ml
124	0.12			
125	4.7	2		
126	0.14			
127	0.056			
128	2.6			
129	0.31	2		
130	0.91			
131	0.1	2		
132	0.084			
133	0.092	2		
134	0.33	2		
135	0.16			
136	0.55	2		
137	1.2			
138	0.34	2		
139	0.96			
140	0.075			
141	0.28			
142	0.29	2		
143	0.097			
144	0.084			
145	2.5			
146	0.099			
147	1.2	2		
148	0.36			

Ex No.	IC50 ( $\mu$ g/ml)	n	% of Control At	
			25 $\mu$ g/ml	50 $\mu$ g/ml
149	0.056			
150	0.28			
151	0.099			
152	1			
153	0.42			
154	1.2			
155	1.1			
156	0.11			
157	>5			
158	0.19			
159	0.38			
160	0.27			
161	2.6			
162	0.78			
163	0.27			
164	0.17			
165	0.96			
166	0.32			
167	0.1			
168	0.11			
169	0.31	4		
170	0.074	11		
171	0.29			
172	0.3			
173	0.3			
174	0.13			

Table 2 (cont)

Ex No.	IC50 ( $\mu$ g/ml)	n	% of Control At	
			25 $\mu$ g/ml	50 $\mu$ g/ml
175	0.038	3		
176	0.1			
177	0.13			
178	0.099	3		
179	0.35			
180	0.81			
181	0.043			
182	1.3			
183	0.078			
184	0.25			
185	0.04			
186	0.034			
187	0.035			
188	0.012	2		
189	0.055			
190	0.33			
191	0.032			
192	>5 a			
193	0.95			
194	0.58			
195	0.1			
196	0.15			
197	0.3			
198	0.091	3		
199	0.38			

Ex No.	IC50 ( $\mu$ g/ml)	n	% of Control At	
			25 $\mu$ g/ml	50 $\mu$ g/ml
200	0.27			
201	0.39			
202	0.25			
203	0.17			
204	0.12			
205	0.036			
206	0.12			
207	0.035			
208	0.014	2		
209	0.11			
210	0.31			
211	0.049	3		
212	0.88			
213	0.47			
214	0.79			
215	3.5			
216	0.63			
217	0.2			
218	>5 a			
219	0.89			
220	4.9			
221	2.8			
222	5	2		
223	2.1			
224	0.3			

Table 2 (cont)

Ex No.	IC50 ( $\mu$ g/ml)	n	% of Control At	
			25 $\mu$ g/ml	50 $\mu$ g/ml
225	0.086			
226	0.095			
227	4.3			
228	>5 a			
229	0.95	2		
230	2.5			
231			44.3	6.6
232			67.5	15.0
233			27.3	20.4
234			5.6	-4.5
235			80.6	14.7
236			28.4	10.9
237			24.1	-3.5
238			100.4	41.5
239			58.8	25.5
240			-0.9	-4.0
241			2.3	2.4
242			13.1	-4.8
243			12.7	-3.0
244			9.2	21.0
245			100.3	72.5
246			4.0	-4.8
247			63.6	46.4
248			15.5	-3.9
249			47.4	20.3

Table 2 (cont)

Ex No.	IC50 ( $\mu$ g/ml)	n	% of Control At	
			25 $\mu$ g/ml	50 $\mu$ g/ml
250			16.4	4.6
251			103.9	28.1
252			94.8	69.6
253			120.0	74.1
254			39.6	15.6
255			58.3	86.1
256			20.2	14.8
257			27.3	-3.5
258			74.6	44.1
259			32.6	0.7
260			87.8	53.5
261			7.4	-3.9
262			23.7	-5.1
263			-1.5	2.0
264			34.5	-4.2
265			8.1	-1.6
266			84.9	72.4
267			17.8	32.1
268			-0.8	4.2
269			3.5	11.9
270	0.095			
271	0.32			
272	0.91			
273	1			
274	1.9			

Table 2 (cont)				
Ex No.	IC50 ( $\mu$ g/ml)	n	% of Control At	
			25 $\mu$ g/ml	50 $\mu$ g/ml
275	0.13			

Notes to Table 2:

- 5    1. n = number of independent assays (n = 1 unless stated otherwise)  
   2. a means that at 5  $\mu$ g/ml the inhibition was between 30 and 50%

### Part 3. Cytotoxicity with H157, U87MG, PC-3 MM2, and DLD1 Cells

The cytotoxicity standard pharmacological test procedure with MTS detection was applied to representative compounds of the invention with four additional human cancer cell lines in order to characterize the range of tumor types against which the compounds were active. The cell lines used were H157 human non-small cell lung carcinoma, U87MG human glioblastoma, PC-3 MM2 human prostate carcinoma, and DLD1 human colon adenocarcinoma. The procedure of the test and the method of data calculation were the same as described above in Part 2 with COLO 205 cells. The results are displayed in Table 3.

Table 3  
 Evaluation of Representative Compounds of the Invention and Standard  
 Cytotoxic Agents in the MTS Cytotoxicity Standard Pharmacological Test  
 Procedure with Four Human Cancer Cell Lines

Example	IC <sub>50</sub> (nM)			
	H157	U87MG	PC-3 MM2	DLD1
35	31	390	220	105
169		>1000	>1000	
170	310	200	140	560
175		180	240	215
178		480	550	
186	38			
187	86			
188	16	48	73	48
198		640	580	
205	83			
208	10	120	140	69
211		370	400	
Camptothecin	10			
Colchicine	13	6.5	10	25
Doxorubicin	17			170
Mitoxantrone	13			
Nocodazole	33	34	43	40
Paclitaxel			0.17	1.4
Vincristine	0.28		0.30	3.0

**Part 4. Cytotoxicity with KB Cells and Drug-Resistant Lines Derived from KB**

- The cytotoxicity standard pharmacological test procedure with MTS detection was applied to representative compounds of the invention with the KB human epidermoid carcinoma cell line and two multidrug resistant lines derived from it. These derived lines were colchicine-resistant KB 8.5, which expresses a moderate level of the multidrug transporter P-glycoprotein, and vinblastine-resistant KB VI, which expresses a high level of P-glycoprotein.
- The purpose of these experiments was to determine if the compounds were able to overcome drug resistance mediated by P-glycoprotein. If the IC<sub>50</sub>'s of the compounds are essentially the same on all three lines, then the compounds are not substrates of P-glycoprotein. If on the other hand, the compounds have much higher IC<sub>50</sub>'s on KB 8.5 and KB VI compared to KB (as do paclitaxel, vincristine, and many other standard anti-cancer drugs) then they would be substrates of P-glycoprotein.

The procedure of the cytotoxicity test and the method of data calculation were the same as described above in Part 2 with COLO 205 cells. The results are displayed in Table 4. The results show that the compounds of this invention have essentially the same IC<sub>50</sub>'s on all three cell lines, indicating that they would not be subject to multidrug resistance mediated by P-glycoprotein.

Table 4  
 Evaluation of Representative Compounds of the Invention and Standard  
 Cytotoxic Agents in the MTS Cytotoxicity Standard Pharmacological Test  
 5 Procedure with Human Cancer Cell Lines that Overexpress the  
 P-glycoprotein Transporter

Example	IC <sub>50</sub> (nM)			Relative Resistance		
	KB	KB 8.5	KB VI	KB	KB 8.5	KB VI
35	19	31	16	1	1.6	0.8
186	30	48	33	1	1.6	1.1
187	45	76	56	1	1.7	1.2
188	10	18	11	1	1.8	1.1
Taxol	<0.03	19	3,325	1	>630	>111,000
Vincristine	<0.06	29	3,150	1	>480	>52,500
Colchicine	7.2	51	1,330	1	7.1	185
Nocodazole	21	24	33	1	1.1	1.6
Doxorubicin	34	101	4,400	1	3.0	130

**Part 5. Cytotoxicity with S1 Cells and a Drug-Resistant Line Derived  
 10 from S1**

The cytotoxicity standard pharmacological test procedure with MTS detection was applied to representative compounds of the invention with the S1 human colon carcinoma cell line and a multidrug resistant line derived from it. The derived line was mitoxantrone-resistant S1-M1, which expresses the multidrug transporter MXR. The purpose of these experiments was to determine representative compounds of the invention able to overcome drug resistance mediated by MXR. If the IC<sub>50</sub>'s of the compounds are essentially the same on both lines, then the compounds are not substrates of MXR. If on the other hand, the compounds have much higher IC<sub>50</sub>'s on S1-M1 compared

to S1 (as do many standard anti-cancer drugs) then they would be substrates of MXR.

The procedure of the cytotoxicity test and the method of data calculation were the same as described above in Part 2 with COLO 205 cells.

- 5 The results are displayed in Table 5. The results show that the compounds of this invention have essentially the same IC<sub>50</sub>'s on both cell lines, indicating that they would not be subject to multidrug resistance mediated by MXR.

10

Table 5

15

Evaluation of Representative Compounds of the Invention and Standard Cytotoxic Agents in the MTS Cytotoxicity Pharmacological Test Procedure with a Human Cancer Cell Line that Overexpresses the MXR Transporter

Protein

Example	IC <sub>50</sub> (nM)		Relative Resistance	
	S1	S1-M1	S1	S1-M1
35	73	94	1	1.3
186	99	102	1	1.0
187	99	124	1	1.3
188	33	74	1	2.2
Colchicine	11	47	1	4.3
Nocodazole	43	146	1	3.4
Doxorubicin	19	10,700	1	565
Mitoxantrone	<4	>10,000	1	>2,500
Camptothecin	6.8	21	1	3.1

INHIBITION OF CELLULAR PROLIFERATION STANDARD  
PHARMACOLOGICAL TEST PROCEDURE USING SULFORHODAMINE B  
AS DETECTION REAGENT

- 5        This standard pharmacological test procedure measures the ability of compounds to inhibit cellular proliferation. Sulforhodamine B staining was used to estimate total cellular protein in each culture after exposure to compounds. A decrease in staining compared to untreated control cultures indicated an inhibition of proliferation.
- 10      Two cell lines were used in these experiments: Reh human acute lymphocytic leukemia, and CCRF-CEM human acute lymphoblastic leukemia, both obtained from ATCC. Two types of experiments were done on each of the two cell lines. In the first, cells were cultured with Example 170 at several concentrations for either 24 or 72 hr, and the effect on cellular proliferation
- 15      was determined. In the second, cells were cultured with Example 170 at several concentrations for 24 hr, the compound was removed and replaced with fresh medium without compound, culture was continued for another 48 hr, and the effect on cellular proliferation was determined. This second experiment determined the ability of cells to recover from the damage inflicted
- 20      by compound during the first 24 hr of culture. At the end of the incubation periods, cells were fixed with trichloroacetic acid and stained with sulforhodamine B using the *in vitro* Toxicology Assay Kit (Sigma). Actinomycin D was used as a positive control in all experiments. Bound dye was measured spectrophotometrically at 565 nm with a reference wavelength
- 25      of 690 nm. Cultures were done in 96-well assay plates with five replicates of each concentration. The absorbance values of the replicates were averaged and expressed as a percent of the vehicle control. Each experiment was repeated once, and the percent of control for a given concentration in each experiment were averaged to calculate the results displayed in Table 6.
- 30      The results showed that Example 170 inhibited the proliferation of both cell lines, with a greater effect observed after 72 hr compared with 24 hr. In

addition, the recovery experiment showed that neither cell line could recover from the toxicity induced by 24 hr of culture with Example 170.

- An additional experiment was done with HL-60 human promyelocytic leukemia in which the inhibition of cellular proliferation by several
- 5 concentrations of Example 170 were determined after 24 or 72 hrs of culture using the Sulforhodamine B test procedure as described above. Concentrations of Example 170 ranged from 0.005-100 µg/ml. The calculated EC<sub>50</sub> value at 24 hr was 2.3 µg/ml, and the EC<sub>50</sub> value at 72 hr was 0.1 µg/ml.

10

15

Table 6  
Evaluation of Example 170 in the Sulforhodamine B Standard Pharmacological Test Procedure with Two Human Leukemia Cell Lines

Conc. ( $\mu\text{g/ml}$ )	Percent of Control					
	Reh Cells			CCRF-CEM Cells		
	24 hr. Treatment	72 hr Treatment	24 hr Treatment 48 hr Recovery	24 hr Treatment	72 hr Treatment	24 hr Treatment 48 hr Recovery
0.005	120.15	88.57	105.29	104.86	94.88	152.66
0.01	110.83	89.43	103.98	111.05	88.98	143.58
0.05	81.50	71.31	81.23	67.31	19.73	57.05
0.1	68.67	65.87	84.68	65.48	24.04	38.99
0.5	67.70	66.24	74.13	65.72	11.59	50.17
1	83.94	52.91	66.81	51.41	20.74	29.42
5	66.21	41.86	61.34	30.04	22.24	28.90
10	71.46	44.70	34.10	42.05	8.17	18.19
50	55.07	35.40	36.36	47.10	24.84	27.16
100	84.35	51.62	35.76	113.70	54.07	39.47
0.2 *	66.99	50.54	39.75	52.44	45.71	20.26

5 \* Actinomycin-D

**CELL CYCLE ANALYSIS STANDARD PHARMACOLOGICAL TEST  
PROCEDURE**

- 10 This standard pharmacological test procedure measures the percentages of cells in a population that are in the G1, S and G2/M phases of the cell cycle. It utilizes staining of fixed cells with propidium iodide and analysis of these cells by flow cytometry. The procedure also gives an estimate of apoptosis induction caused by drug treatment by measurement of 15 the appearance of particles with sub-G1 amounts of DNA. Microtubule-active

drugs characteristically arrest cells in the G2/M phase of the cell cycle because of disruption of the function of the microtubules that comprise the mitotic spindle.

HeLa cells were maintained in RPMI-1640 medium with L-glutamine,  
5 supplemented with 10% heat-inactivated fetal calf serum, 100 units/ml  
penicillin, and 100 µg/ml streptomycin. For assay, cells were harvested by  
trypsinization, washed, counted and distributed to wells of a 6-well plate at  
50,000 cells per well in 3 ml of medium. Cells were cultured overnight at 37°  
in humidified 5% CO<sub>2</sub> in air.

10 On day 2, compounds for test were diluted and added to wells at the  
final concentrations given in the tables. Twenty hours after drug addition,  
cells from each well were harvested, fixed with cold 80% ethanol, treated with  
100 µg/ml RNase and stained with propidium iodide before analysis by flow  
cytometry. The percentages of total cells in G1, S, G2/M, and apoptosis (sub-  
15 G1 population) were estimated from the fluorescence histograms, and  
compared with those determined using untreated control cells in the same  
assay.

Table 7 displays results for representative compounds of this invention  
tested at a low concentration and at a five-fold higher concentration. Table 8  
20 displays results of a second experiment in which representative compounds  
were tested at six concentration levels each. In both experiments the  
compounds caused a profound increase in the percentage of cells in the  
G2/M phase of the cell cycle and induced substantial apoptosis.

Table 7

Evaluation of Representative Compounds of the Invention in the Cell Cycle Analysis Standard Pharmacological Test Procedure with HeLa Cells

Example	Conc. ( $\mu$ g/mL)	Percent Cell Cycle Phase			
		Apop	G1	S	G2/M
None	-	3	64	18	16
	-	2	63	18	17
1	0.84	8	3	10	79
	4.2	13	7	12	68
5	0.057	44	10	22	25
	0.285	9	1	5	85
7	0.12	8	2	6	84
	0.6	9	3	8	81
9	0.86	10	2	7	81
	4.3	16	28	21	35
12	0.27	46	10	18	26
	1.35	7	1	7	85
27	0.033	28	4	13	55
	0.165	8	1	5	86
35	0.022	28	5	14	54
	0.11	-	-	-	-
39	2.19	26	4	15	55
	10.95	19	17	20	45
41	0.062	9	58	20	13
	0.31	34	18	17	30
42	0.33	47	14	20	19
	1.65	6	1	10	83
47	0.11	8	2	8	83
	0.55	7	1	10	81

Table 7 continued

Example	Conc. ( $\mu\text{g/mL}$ )	Percent Cell Cycle Phase			
		Apop	G1	S	G2/M
59	0.18	43	8	24	26
	0.9	8	2	6	84
61	0.08	7	1	9	83
	0.4	7	2	8	83
105	0.08	12	3	11	74
	0.4	6	2	8	84
127	0.08	8	2	12	79
	0.4	6	3	6	84
151	0.08	15	4	14	67
	0.4	9	6	8	76
186	0.08	7	2	8	82
	0.4	7	2	10	80
187	0.08	6	4	9	81
	0.4	7	2	9	81
188	0.08	9	2	8	81
	0.4	9	2	10	78

Note to Table 6: Apop = Apoptosis

Table 8

Evaluation of Representative Compounds of the Invention in the Cell Cycle  
Analysis Standard Pharmacological Test Procedure with HeLa Cells

Example	Conc. ( $\mu$ g/mL)	Percent Cell Cycle Phase			
		Apop	G1	S	G2/M
None	-	4	55	23	18
	-	3	49	25	20
	-	1	56	20	20
35	0.001	1	57	22	20
	0.003	1	58	22	18
	0.01	2	57	20	21
	0.03	29	20	25	25
	0.1	26	9	13	50
	0.3	4	4	3	89
	133	0.01	4	54	19
133	0.03	28	25	21	25
	0.1	34	9	26	29
	0.3	15	5	8	73
	1	3	4	3	90
	3	3	4	3	89
	169	0.01	2	51	23
169	0.03	14	41	21	24
	0.1	33	17	23	25
	0.3	34	8	24	32
	1	3	5	3	88
	3	4	5	2	88

Example	Conc. ( $\mu\text{g/mL}$ )	Percent Cell Cycle Phase			
		Apop	G1	S	G2/M
170	0.01	13	42	21	24
	0.03	33	17	20	28
	0.1	27	3	18	50
	0.3	5	5	4	85
	1	3	4	4	88
	3	3	4	4	88
188	0.001	1	55	21	23
	0.003	2	56	18	23
	0.01	18	35	19	27
	0.03	27	7	14	52
	0.1	4	4	3	88
	0.3	3	3	3	90
208	0.001	2	59	20	20
	0.003	2	57	20	21
	0.01	14	43	20	23
	0.03	33	8	21	36
	0.1	3	2	3	90
	0.3	3	3	2	91

Note to Table 7: Apop = Apoptosis

**TUBULIN POLYMERIZATION STANDARD PHARMACOLOGICAL TEST**  
**PROCEDURE USING HIGHLY PURIFIED TUBULIN**

This standard pharmacological test procedure determines the activity  
5 of representative compounds of this invention in promoting the polymerization  
of  $\alpha/\beta$  tubulin heterodimers. The tubulin preparation used was over 99% pure  
so that any effects of test compounds on polymerization must be due to direct  
binding of the test compounds to tubulin protein. It is well known that in this  
assay paclitaxel promotes polymerization compared to the control reaction  
10 without drug, and that vincristine and colchicine inhibit polymerization. Highly  
purified tubulin does not exhibit substantial spontaneous polymerization at  
protein concentrations between 1 and 2 mg/ml. Therefore an agent such as  
glycerol is added to the reactions to lower the critical concentration for  
polymerization and yield a higher spontaneous control polymerization. In  
15 some experiments described below, either glycerol or guanosine 5'-  
triphosphate (the energy source of polymerization) was left out of the reaction  
mixtures in order to better compare the effects of paclitaxel and  
representative compounds of this invention.

20 **Part 1. Polymerization of Purified Tubulin in the Presence of**  
**Guanosine 5'-triphosphate and Glycerol**

Bovine brain tubulin, purchased from Cytoskeleton, Inc., was greater  
than 99% pure by polyacrylamide gel electrophoresis. The protein was  
dissolved at 1.5 mg/ml in ice-cold GPEM buffer (80 mM piperazine-N,N'-bis[2-  
25 ethanesulfonic acid], pH 6.9, 1 mM ethylene glycol-bis( $\beta$ -aminoethyl ether)-  
N,N,N',N'-tetraacetic acid, 1 mM magnesium chloride, 1 mM guanosine 5'-  
triphosphate, GTP) containing 10% (w/w) glycerol. The solution was  
centrifuged at top speed in an Eppendorf model 5415C microfuge for 10 min  
at 4° immediately before use. The tubulin solution was added to wells of a  $\frac{1}{2}$   
area 96-well plate (Costar No. 3696) already containing the compounds of

interest. Each compound was assayed at three concentrations as indicated. Final volume per well was 110  $\mu$ l. Each sample was done in duplicate, and the control reaction, which received drug solvent only, was done in quadruplicate. The highest concentration of DMSO in any reaction was 1%.

- 5      The plate was put in a Molecular Devices SpectraMax plate reader thermostated at 35° and the absorbance of each well at 340 nm was determined every minute for 60 minutes. The absorbance at time 0 for each well was subtracted from each of the subsequent absorbance readings for that well, and then the duplicates were averaged.
- 10     The results of this standard pharmacological test procedure with representative compounds of this invention and with standard microtubule-active drugs are displayed in Tables 9 to 14. Compounds that enhanced the rate and/or extent of purified tubulin polymerization compared to the control (as does paclitaxel) were judged to be promoters of polymerization;
- 15     compounds that reduced the rate or extent of polymerization (e.g., vincristine, colchicine) were judged to be inhibitors.

**Table 9**  
**Evaluation of Examples 35 and 188 in the Tubulin Polymerization**  
**Standard Pharmacological Test Procedure**

Time (min)	$\Delta A_{340}$						
	Example 35			Example 188			
	10 $\mu M$	1 $\mu M$	0.1 $\mu M$	10 $\mu M$	1 $\mu M$	0.1 $\mu M$	
0	0	0	0	0	0	0	0
5	0.0434	0.0003	0.0004	0.0179	-0.0007	-0.0006	-0.0009
10	0.0972	0.0015	0.0010	0.0469	0.0001	-0.0005	-0.0008
15	0.1219	0.0028	0.0012	0.0667	0.0016	-0.0001	0.0001
20	0.1316	0.0058	0.0024	0.0813	0.0040	0.0009	0.0019
25	0.1364	0.0079	0.0041	0.0919	0.0063	0.0026	0.0051
30	0.1387	0.0106	0.0061	0.0988	0.0110	0.0052	0.0087
35	0.1397	0.0139	0.0079	0.1032	0.0141	0.0079	0.0132
40	0.1401	0.0177	0.0099	0.1064	0.0179	0.0119	0.0198
45	0.1392	0.0232	0.0133	0.1100	0.0229	0.0142	0.0221
50	0.1396	0.0278	0.0167	0.1149	0.0288	0.0203	0.0245
55	0.1399	0.0311	0.0193	0.1165	0.0337	0.0262	0.0282
60	0.1398	0.0350	0.0224	0.1176	0.0372	0.0304	0.0340

Table 10

Evaluation of Example 170 and Paclitaxel in the Tubulin Polymerization  
 Standard Pharmacological Test Procedure

$\Delta A_{340}$							
	Example 170			Paclitaxel			<u>Control</u>
Time (min)	10 $\mu M$	1 $\mu M$	0.1 $\mu M$	10 $\mu M$	1 $\mu M$	0.1 $\mu M$	
0	0	0	0	0	0	0	0
5	0.0103	-0.0001	-0.0005	0.0136	0.0044	-0.0012	-0.0009
10	0.0555	0.0008	-0.0010	0.0416	0.0167	-0.0010	-0.0008
15	0.0923	0.0028	-0.0005	0.0704	0.0336	0.0001	0.0001
20	0.1100	0.0056	0.0002	0.0931	0.0500	0.0025	0.0019
25	0.1199	0.0093	0.0018	0.1075	0.0638	0.0060	0.0051
30	0.1257	0.0143	0.0041	0.1162	0.0748	0.0100	0.0087
35	0.1289	0.0198	0.0053	0.1216	0.0835	0.0123	0.0132
40	0.1330	0.0246	0.0088	0.1245	0.0903	0.0168	0.0198
45	0.1353	0.0291	0.0124	0.1269	0.0957	0.0229	0.0221
50	0.1353	0.0338	0.0155	0.1279	0.0997	0.0257	0.0245
55	0.1363	0.0380	0.0192	0.1279	0.1027	0.0293	0.0282
60	0.1364	0.0419	0.0241	0.1282	0.1053	0.0314	0.0340

0989575.002901

Table 11

Evaluation of Examples 169 and 175 in the Tubulin Polymerization  
Standard Pharmacological Test Procedure

$\Delta A_{340}$							
	Example 169			Example 175			Control
Time (min)	10 $\mu M$	1 $\mu M$	0.1 $\mu M$	10 $\mu M$	1 $\mu M$	0.1 $\mu M$	
0	0	0	0	0	0	0	0
5	0.0239	0.0005	-0.0014	0.0073	0.0001	-0.0012	-0.0012
10	0.1172	0.0011	-0.0009	0.0199	0.0014	-0.0005	-0.0011
15	0.1435	0.0024	0.0001	0.0309	0.0037	0.0011	0.0000
20	0.1509	0.0045	0.0020	0.0399	0.0067	0.0025	0.0024
25	0.1532	0.0073	0.0042	0.0488	0.0102	0.0057	0.0051
30	0.1548	0.0106	0.0057	0.0566	0.0160	0.0088	0.0108
35	0.1554	0.0154	0.0105	0.0638	0.0217	0.0116	0.0157
40	0.1555	0.0197	0.0136	0.0704	0.0294	0.0177	0.0203
45	0.1552	0.0246	0.0186	0.0761	0.0349	0.0233	0.0246
50	0.1545	0.0331	0.0234	0.0817	0.0416	0.0261	0.0329
55	0.1561	0.0414	0.0282	0.0872	0.0450	0.0309	0.0369
60	0.1552	0.0456	0.0322	0.0919	0.0485	0.0373	0.0392

Table 12

Evaluation of Example 178 and Paclitaxel in the Tubulin  
Polymerization Standard Pharmacological Test Procedure

Time (min)	$\Delta A_{340}$						
	Example 178			Paclitaxel			Control
	10 $\mu M$	1 $\mu M$	0.1 $\mu M$	10 $\mu M$	1 $\mu M$	0.1 $\mu M$	
0	0	0	0	0	0	0	0
5	0.0182	-0.0029	-0.0001	0.0200	0.0024	-0.0008	-0.0012
10	0.0304	-0.0021	0.0000	0.0587	0.0144	0.0005	-0.0011
15	0.0448	-0.0007	0.0002	0.0939	0.0315	0.0031	0.0000
20	0.0602	0.0006	0.0009	0.1199	0.0484	0.0070	0.0024
25	0.0770	0.0039	0.0030	0.1369	0.0626	0.0103	0.0051
30	0.0951	0.0064	0.0055	0.1470	0.0746	0.0159	0.0108
35	0.1099	0.0110	0.0080	0.1522	0.0838	0.0197	0.0157
40	0.1250	0.0152	0.0134	0.1557	0.0913	0.0256	0.0203
45	0.1360	0.0202	0.0216	0.1583	0.0969	0.0304	0.0246
50	0.1424	0.0242	0.0218	0.1584	0.1014	0.0336	0.0329
55	0.1488	0.0273	0.0229	0.1588	0.1050	0.0368	0.0369
60	0.1538	0.0316	0.0299	0.1586	0.1076	0.0399	0.0392

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Table 13

Evaluation of Examples 198 and 211 and Paclitaxel in the Tubulin  
Polymerization Standard Pharmacological Test Procedure

*	$\Delta A_{340}$									
	Example 198			Example 211			Paclitaxel			**
	10 $\mu M$	1 $\mu M$	0.1 $\mu M$	10 $\mu M$	1 $\mu M$	0.1 $\mu M$	10 $\mu M$	1 $\mu M$	0.1 $\mu M$	
0	0	0	0	0	0	0	0	0	0	0
5	0.0011	0.0001	0.0021	-0.0008	-0.0019	-0.0001	0.0145	0.0037	-0.0014	-0.0012
10	0.0025	0.0006	0.0053	-0.0006	-0.0017	0.0014	0.0496	0.0173	0.0032	-0.0014
15	0.0057	0.0017	0.0096	0.0009	0.0000	0.0043	0.0857	0.0381	0.0056	-0.0001
20	0.0117	0.0046	0.0143	0.0029	0.0027	0.0080	0.1119	0.0572	0.0098	0.0031
25	0.0206	0.0071	0.0200	0.0055	0.0060	0.0129	0.1280	0.0731	0.0160	0.0077
30	0.0303	0.0106	0.0239	0.0085	0.0107	0.0173	0.1370	0.0860	0.0217	0.0124
35	0.0407	0.0153	0.0292	0.0121	0.0138	0.0228	0.1427	0.0961	0.0289	0.0193
40	0.0489	0.0214	0.0367	0.0165	0.0195	0.0287	0.1462	0.1041	0.0360	0.0223
45	0.0572	0.0258	0.0393	0.0211	0.0251	0.0321	0.1483	0.1102	0.0431	0.0288
50	0.0661	0.0320	0.0495	0.0263	0.0279	0.0397	0.1495	0.1148	0.0488	0.0345
55	0.0729	0.0360	0.0556	0.0320	0.0339	0.0458	0.1505	0.1185	0.0544	0.0389
60	0.0763	0.0413	0.0607	0.0383	0.0393	0.0512	0.1508	0.1211	0.0596	0.0440

\* Time (min)

\*\* Control

Table 14

Evaluation of Vincristine, Colchicine, and Paclitaxel in the Tubulin  
Polymerization Standard Pharmacological Test Procedure

	$\Delta A_{340}$									
	Vincristine			Colchicine			Paclitaxel			**
	*	10 $\mu\text{M}$	1 $\mu\text{M}$	0.1 $\mu\text{M}$	10 $\mu\text{M}$	1 $\mu\text{M}$	0.1 $\mu\text{M}$	10 $\mu\text{M}$	1 $\mu\text{M}$	
0	0*	0	0	0	0	0	0	0	0	0
5	-0.0011	-0.0008	0.0016	0.0005	-0.0003	-0.0011	0.0104	0.0023	-0.0008	-0.0016
10	0.0001	-0.0007	0.0012	0.0011	0.0000	-0.0012	0.0372	0.0128	0.0020	-0.0013
15	-0.0001	-0.0007	0.0018	0.0006	0.0002	-0.0008	0.0658	0.0288	0.0084	0.0007
20	-0.0006	-0.0001	0.0031	-0.0001	0.0009	0.0003	0.0885	0.0434	0.0107	0.0027
25	-0.0012	0.0003	0.0044	-0.0003	0.0019	0.0024	0.1040	0.0568	0.0160	0.0054
30	-0.0015	0.0012	0.0074	-0.0008	0.0029	0.0058	0.1149	0.0682	0.0251	0.0103
35	-0.0018	0.0019	0.0119	-0.0008	0.0039	0.0086	0.1218	0.0779	0.0321	0.0181
40	-0.0017	0.0029	0.0154	-0.0012	0.0044	0.0119	0.1281	0.0857	0.0366	0.0232
45	-0.0020	0.0041	0.0189	-0.0016	0.0057	0.0159	0.1299	0.0920	0.0423	0.0272
50	-0.0025	0.0057	0.0253	-0.0020	0.0067	0.0209	0.1313	0.0975	0.0480	0.0300
55	-0.0026	0.0067	0.0298	-0.0020	0.0079	0.0243	0.1325	0.1015	0.0517	0.0362
60	-0.0026	0.0079	0.0322	-0.0021	0.0090	0.0274	0.1335	0.1049	0.0550	0.0399

\* Time (min)

\*\* Control

Part 2.Polymerization of Purified Tubulin in the Absence of Either Guanosine 5'-triphosphate or Glycerol

This standard pharmacological test procedure measures the ability of a representative example of the invention to induce polymerization of purified tubulin in the absence of glycerol or guanosine 5'-triphosphate (GTP). All other conditions and data calculation were as given above in Part 1.

In the first experiment, the polymerization reaction mixture did not contain glycerol. In the absence of glycerol, highly purified tubulin undergoes very little spontaneous polymerization but paclitaxel is known to induce polymerization under these conditions. The data displayed in Table 15 show that Example 170 also induced polymerization in the absence of glycerol.

In the second experiment, GTP was absent from the reaction mixture. Normal tubulin polymerization requires energy released from GTP hydrolysis to drive subunit assembly, but paclitaxel is able to induce polymer formation even in the absence of GTP. The data displayed in Table 16 show that Example 170 also induced polymerization in the absence of GTP.

The results of both these experiments are consistent with the conclusion that Example 170 has a paclitaxel-like mechanism of action on tubulin polymerization.

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Table 15

Evaluation of Example 170 and Paclitaxel in the Tubulin Polymerization Standard Pharmacological Test Procedure in the absence of glycerol

Time (min)	$\Delta A_{340}$				
	Example 170		Paclitaxel		<i>Control</i>
	10 $\mu M$	1 $\mu M$	10 $\mu M$	1 $\mu M$	
0	0	0	0	0	0
5	0.0019	0.0005	0.0056	0.0014	0.0002
10	0.0049	0.0014	0.0279	0.0091	0.0007
15	0.0095	0.0024	0.0546	0.0198	0.0011
20	0.0153	0.0039	0.0801	0.0310	0.0018
25	0.0215	0.0054	0.1016	0.0412	0.0024
30	0.0280	0.0074	0.1188	0.0500	0.0033
35	0.0347	0.0097	0.1070	0.0576	0.0043
40	0.0422	0.0121	0.1142	0.0638	0.0048
45	0.0504	0.0149	0.1192	0.0691	0.0058
50	0.0595	0.0188	0.1238	0.0737	0.0069
55	0.0687	0.0222	0.1262	0.0773	0.0077
60	0.0783	0.0264	0.1293	0.0805	0.0094

Table 16

Evaluation of Example 170 and Paclitaxel in the Tubulin Polymerization Standard Pharmacological Test Procedure in the absence of GTP

Time (min)	$\Delta A_{340}$				
	Example 170		Paclitaxel		<u>Control</u>
	20 $\mu M$	5 $\mu M$	20 $\mu M$	5 $\mu M$	
0	0	0	0	0	0
5	0.0364	0.0000	0.0204	0.0032	-0.0010
10	0.0582	0.0009	0.0592	0.0160	-0.0004
15	0.0735	0.0028	0.0933	0.0305	0.0019
20	0.0830	0.0046	0.1159	0.0445	0.0035
25	0.0921	0.0078	0.1288	0.0570	0.0078
30	0.1022	0.0107	0.1365	0.0674	0.0121
35	0.1086	0.0142	0.1409	0.0764	0.0167
40	0.1125	0.0180	0.1435	0.0843	0.0198
45	0.1192	0.0220	0.1449	0.0908	0.0241
50	0.1225	0.0265	0.1457	0.0962	0.0276
55	0.1264	0.0310	0.1456	0.1008	0.0333
60	0.1277	0.0357	0.1455	0.1046	0.0387

**IMMUNOFLUORESCENCE STANDARD TEST PROCEDURE FOR  
ANALYSIS OF EFFECTS OF COMPOUNDS ON MORPHOLOGY OF  
MITOTIC SPINDLE MICROTUBULES IN CELLS**

5 Compounds that bind to tubulin or microtubules typically have profound and characteristic effects on the structure of the microtubules which comprise the mitotic spindle of dividing cells. Compounds such as vincristine and colchicine that inhibit normal tubulin polymerization cause a severe disruption and even disappearance of spindle microtubules. On the other hand, 10 compounds such as paclitaxel that promote tubulin polymerization and stabilize microtubules cause the appearance of dense tubulin bundles or aggregates. These effects of compounds can be visualized by immunofluorescent staining of fixed cells.

15 PC-3 MM2 human prostate carcinoma cells were plated at 5 X 10<sup>4</sup> cells/chamber in 8-chamber microscope slides that had been treated with poly-D-lysine (Biocoat 8-well CultureSlide, Becton Dickinson). The cells were allowed to attach and grow for 24 hr before addition of compounds at the indicated concentrations. After an additional 18-20 hr of culture with 20 compounds, cells were fixed directly on the slides with methanol at minus 20°, rehydrated in phosphate-buffered saline, and stained with a mouse monoclonal antibody to  $\alpha$ -tubulin (clone DM 1A, Sigma) followed by F(ab')<sub>2</sub> fragments of goat anti-mouse IgG, FITC conjugate (Jackson Immunoresearch). Cells were also stained with Hoescht 33258 to visualize DNA. Cells were viewed with a Zeiss fluorescence microscope under epi- 25 illumination, and digital images were captured with a MTI Model DC330 video camera using Optimas V software. Images were processed using Corel PhotoPaint.

As displayed in Table 17, representative compounds of this invention produced marked bundling or aggregation of spindle microtubules in dividing

cells. The patterns of microtubule bundling were similar to that produced by paclitaxel. When tested at equi-potent concentrations (i.e., at a concentration of each compound equal to eight times its IC<sub>50</sub> value in the 3-day MTS cytotoxicity assay), paclitaxel produced predominantly bipolar structures in  
5 which the microtubules appeared to be shortened and condensed. The compounds of this invention typically produced two, three, or four dense, circular bundles with intense fluorescence. The microtubule disrupting agents, vincristine and colchicine, produced patterns that were quite distinct from the compounds described here. These results are consistent with the  
10 conclusion that the compounds of this invention promote tubulin polymerization, as does paclitaxel.

5

**Table 17**  
**Evaluation of Representative Compounds of this Invention on Morphology of  
 Mitotic Spindle Microtubules in PC-3 MM2 Cells Determined by the  
 Immunofluorescence Standard Pharmacological Test Procedure**

Ex.	Concentration ( $\mu$ M)	Appearance of Mitotic Spindle Microtubules
35	0.54	Less tightly condensed, greater variety of abnormal structures, including "tangled spaghetti"
169	6.41	Dense, compact, highly fluorescent bundles, roughly circular in shape, 2-4 per cell
170	1.74	Dense, compact, highly fluorescent bundles, roughly circular in shape, 2-4 per cell
175	0.74	Dense, compact, highly fluorescent bundles, roughly circular in shape, 2-4 per cell
178	1.91	Rigid spikes emanating from a central core: "sea urchin" appearance
188	0.24	Dense, compact, highly fluorescent bundles, roughly circular in shape, 2-4 per cell
198	2.10	Dense, compact, highly fluorescent bundles, roughly circular in shape, 2-4 per cell
208	0.26	Dense, compact, highly fluorescent bundles, roughly circular in shape, up to 8 per cell
211	0.89	Dense, compact, highly fluorescent bundles, roughly circular in shape, 2-4 per cell
Paclitaxel	0.016	Dense, compact, highly fluorescent bundles, typically bipolar
Vincristine	0.008	Multiple abnormal structures, many resembling partially disrupted spindles
Colchicine	0.064	Almost completely depolymerized microtubules, sometimes with multiple small flecks of brighter fluorescence

**STANDARD PHARMACOLOGICAL TEST PROCEDURE OF ANTITUMOR  
ACTIVITY IN ATHYMIC MICE BEARING HUMAN TUMOR XENOGRAFTS**

The tumors used were H157 human non-small cell lung carcinoma,  
5 U87MG human glioblastoma, LOX human melanoma, and DLD1 human  
colon adenocarcinoma. Cells were cultured in RPMI-1640 medium with  
L-glutamine, supplemented with 10% heat-inactivated fetal calf serum, 100  
units/ml penicillin and 100 µg/ml streptomycin. Cells were injected  
subcutaneously into the flank of outbred nu/nu mice. About 5 days later  
10 tumors were staged and those around 100 mg were selected for use. Tumor  
weights were calculated from measurements of length in two dimensions.

Compounds for test were prepared in Klucel and administered to mice  
by intraperitoneal injection (0.5 ml volume) or by oral gavage (0.2 ml volume).  
Typically, the compounds of this invention were given twice per day for 14  
15 days at the doses indicated in the tables. Each experimental group contained  
10 animals unless otherwise indicated. The control group (also 10 animals)  
received Klucel only. Tumor weights were estimated every 3 to 5 days in  
most experiments (every 7 days in one experiment).

Individual experiments are displayed in Tables 18-28.

Table 18

Evaluation of Example 170 on Growth of Human H157 Non-small Cell Lung Carcinoma in Athymic Mice: Comparison of Intrapерitoneal and Oral Dosing

Treatment	Parameter	Day 0	Day 7	Day 10	Day 14	Day 16	Day 18	Day 21
Klucel	MTW	121	509	756	1298	1583	1752	2879
Ex. 170 25 mg/kg bid, ip	MTW	128	221	287	567	755	1163	2467
	T/C	1.05	0.43	0.38	0.44	0.48	0.66	0.86
	p		0.001	0.001	0.001	0.009	0.062	0.282
Ex. 170 25 mg/kg bid, po	MTW	125	191	235	489	591	816	1835
	T/C	1.03	0.37	0.31	0.38	0.37	0.47	0.64
	p		0.0005	0.0003	0.0003	0.0025	0.0065	0.052

5

## Notes:

1. MTW = mean tumor weight = mean weight of tumors in all animals of the group.  
Each group had 10 animals.
- 10 2. Animals were staged on day 0 and dosed on days 1-14.
3. T/C = MTW of treated animals on day n/MTW of control animals on day n.
4. p = p value, Student's T-test.
5. No deaths in experimental groups.

Table 19  
 Evaluation of Example 170 on Growth of Human H157 Non-small  
 Cell Lung Carcinoma in Athymic Mice:  
 Comparison of Oral Dosing at Three Levels

Treatment	Parameter	Day 0	Day 4	Day 8	Day 12	Day 14	Day 17
Klucel	MTW	117	270	549	1066	1632	2314
Ex. 170 25 mg/kg bid, po	MTW	127	142	194	428	602	839
	T/C	1.08	0.53	0.35	0.40	0.37	0.36
	p		0.002	0.001	0.003	0.001	0.001
Ex. 170 12.5 mg/kg bid, po	MTW	126	188	275	464	748	965
	T/C	1.08	0.70	0.50	0.44	0.46	0.42
	p		0.018	0.005	0.004	0.004	0.002
Ex. 170 6.3 mg/kg bid, po	MTW	121	221	377	643	1030	1147
	T/C	1.03	0.82	0.69	0.60	0.63	0.50
	p		0.130	0.044	0.023	0.024	0.003

5

Notes:

1. MTW = mean tumor weight = mean weight of tumors in all animals of the group.  
 Each group had 10 animals.
2. Animals were staged on day 0 and dosed on days 1-14.
- 10 3. T/C = MTW of treated animals on day n/MTW of control animals on day n.
4. p = p value, Student's T-test.
5. One death each in 25 and 12.5 groups.

Table 20

## Evaluation of Example 170 on Growth of Human H157 Non-small Cell

Lung Carcinoma in Athymic Mice:

5

## Comparison of Oral Dosing Once or Twice Per Day

Treatment	Parameter	Day 0	Day 4	Day 9	Day 12	Day 14	Day 18
Klucel	MTW	111	334	577	1037	2237	3782
Ex. 170 25 mg/kg qd, po	MTW	126	219	287	431	766	1550
	T/C	1.14	0.65	0.50	0.42	0.34	0.41
	p		0.03	0.01	0.0006	0.0006	0.005
Ex. 170 25 mg/kg bid, po	MTW	115	123	158	176	413	817
	T/C	1.04	0.37	0.27	0.17	0.18	0.22
	p		4E-05	5E-05	2E-06	9E-06	2.5E-05

## Notes:

1. MTW = mean tumor weight = mean weight of tumors in all animals of the group.  
Each group had 10 animals.
- 10 2. Animals were staged on day 0 and dosed on days 1-14.
3. T/C = MTW of treated animals on day n/MTW of control animals on day n.
4. p = p value, Student's T-test.
5. No deaths in experimental groups.

Table 21

Evaluation of Example 170, Example 169, and Example 133 on Growth of Human H157 Non-small Cell Lung Carcinoma in Athymic Mice:

Treatment	Parameter	Day 0	Day 5	Day 7	Day 10	Day 14	Day 17
Klucel	MTW	119	300	425	638	1385	1940
Ex. 170 25 mg/kg bid, ip	MTW	136	215	253	345	540	1203
	T/C	1.14	0.72	0.60	0.54	0.39	0.62
	p		0.07	0.05	0.07	0.03	0.10
Ex. 169 25 mg/kg bid, ip	MTW	136	277	425	716	1641	1869
	T/C	1.14	0.92	1.00	1.12	1.18	0.96
Ex. 133 25 mg/kg bid, ip	MTW	139	262	367	558	1103	1888
	T/C	1.17	0.87	0.86	0.87	0.80	0.97

5

Notes:

1. MTW = mean tumor weight = mean weight of tumors in all animals of the group.  
Each group had 10 animals.
- 10 2. Animals were staged on day 0 and dosed on days 1-14.
3. T/C = MTW of treated animals on day n/MTW of control animals on day n.
4. p = p value, Student's T-test.
5. One death in Example 170 group.

Table 22  
Evaluation of Example 170 and Example 208 on Growth of Human H157  
Non-small Cell Lung Carcinoma in Athymic Mice

Treatment	Parameter	Day 0	Day 3	Day 7	Day 10	Day 14	Day 17	Day 21
Klucel	MTW	138	213	580	1028	1948	3041	3453
Ex. 170 50 mg/kg bid, then qd, ip	MTW	159	123	162	236	391	562	1335
	T/C	1.15	0.58	0.28	0.23	0.20	0.18	0.39
	p		0.002	0.0005	0.001	0.001	0.0005	0.006
Ex. 208 50 mg/kg bid, then qd,ip	MTW	158	187	287	367	See note 5	See note 5	See note 5

5

Notes:

1. MTW = mean tumor weight = mean weight of tumors in all animals of the group.  
Each group had 10 animals.
- 10 2. Animals were staged on day 0 and dosed on days 1-14. Dosing was bid days 1-6, then qd days 7-14.
3. T/C = MTW of treated animals on day n/MTW of control animals on day n.
4. p = p value, Student's T-test.
5. Dosing of Example 208 was stopped after 10 days because of toxicity.
- 15 6. 1 death in Example 170 group.

Table 23  
 Evaluation of Example 35 on Growth of Human H157  
 Non-small Cell Lung Carcinoma in Athymic Mice

Treatment	Parameter	Day 0	Day 6	Day 10	Day 14	Day 18	Day 21	Day 25
Klucel	MTW	87	255	334	721	1212	1148	2076
Ex. 35 50 mg/kg bid, ip	MTW	91	305	514	1372	2192	2296	2154
	T/C	1.05	1.20	1.54	1.90	1.81	2.00	1.04
	p							

5 Notes:

1. MTW = mean tumor weight = mean weight of tumors in all animals of the group.  
 Each group had 10 animals.
2. Animals were staged on day 0 and dosed on days 1-14
- 10 3. T/C = MTW of treated animals on day n/MTW of control animals on day n.
4. p = p value, Student's T-test.
5. No deaths in experimental group.

Table 24

Evaluation of Example 188 on Growth of Human H157 Non-small Cell Lung Carcinoma in Athymic Mice

Treatment	Parameter	Day 0	Day 4	Day 7	Day 10
Klucel	MTW	139	325	516	942
Ex. 188 50 mg/kg bid, ip	MTW	154	385	560	1037
	T/C	1.11	1.18	1.08	1.10
	p		0.15	0.33	0.31

5

Notes:

1. MTW = mean tumor weight = mean weight of tumors in all animals of the group.  
Each group had 10 animals.
2. Animals were staged on day 0 and dosed on days 1-10.
3. T/C = MTW of treated animals on day n/MTW of control animals on day n.
4. p = p value, Student's T-test.
5. Dosing of Example 188 was stopped after 10 days because of toxicity.

Table 25  
 Evaluation of Example 170 on Growth of Human U87MG  
 Glioblastoma in Athymic Mice: Comparison of Intraperitoneal  
 Dosing at Three Levels

Treatment	Parameter	Day 0	Day 4	Day 7	Day 10	Day 14	Day 17	Day 19
Klucel	MTW	160	258	406	504	1025	1656	2257
Ex. 170 25 mg/kg bid, ip	MTW	156	134	145	111	144	200	296
	T/C	0.98	0.52	0.36	0.22	0.14	0.12	0.13
	p		2E-07	8.8E-07	1.5E-08	6.9E-09	3.3E-09	2.8E-06
Ex. 170 10 mg/kg bid, ip	MTW	156	190	232	314	664	1155	1896
	T/C	0.98	0.74	0.57	0.62	0.65	0.70	0.84
	p		0.0010	0.0001	0.0005	0.0027	0.0084	0.174
Ex. 170 5 mg/kg bid, ip	MTW	161	213	320	414	849	1631	2567
	T/C	1.01	0.83	0.79	0.82	0.83	0.99	1.14
	p		0.028	0.052	0.100	0.157	0.462	0.259

5

Notes:

1. MTW = mean tumor weight = mean weight of tumors in all animals of the group.  
 Each group had 10 animals.
- 10 2. Animals were staged on day 0 and dosed on days 1-14.
3. T/C = MTW of treated animals on day n/MTW of control animals on day n.
4. p = p value, Student's T-test.
5. No deaths in experimental groups.

Table 26  
 Evaluation of Representative Compounds of this Invention on  
 Growth of Human U87MG Glioblastoma in Athymic Mice

Treatment	Parameter	Day 0	Day 3	Day 7	Day 9
Klucel	MTW	128	213	363	537
Ex. 170 25 mg/kg bid, ip	MTW	128	138	120	112
	T/C	1.00	0.65	0.33	0.21
Ex. 211 25 mg/kg bid, ip	MTW	130	171	266	374
	T/C	1.02	0.80	0.73	0.70
Ex. 198 25 mg/kg bid, ip	MTW	127	198	305	559
	T/C	0.99	0.93	0.84	1.04
Ex. 178 25 mg/kg bid, ip	MTW	124	112	See note 4	See note 4
	T/C	0.97	0.53		

Table 26 Continued  
 Evaluation of Representative Compounds of this Invention on Growth of  
 Human U87MG Glioblastoma in Athymic Mice

Treatment	Parameter	Day 0	Day 3	Day 7	Day 9
Klucel	MTW	128	213	363	537
Ex. 175 25 mg/kg bid, ip	MTW	138	176	239	433
	T/C	1.08	0.83	0.66	0.81
Ex. 35 25 mg/kg bid, ip	MTW	135	180	226	427
	T/C	1.05	0.85	0.62	0.80
Ex. 169 25 mg/kg bid, ip	MTW	136	187	254	464
	T/C	1.06	0.88	0.70	0.86

5

Notes:

1. MTW = mean tumor weight = mean weight of tumors in all animals of the group.  
 Each group had 10 animals.
2. Animals were staged on day 0 and dosed on days 1-9.
3. T/C = MTW of treated animals on day n/MTW of control animals on day n.
4. Dosing of Example 178 was stopped after 4 days because of toxicity.

Table 27

Evaluation of Example 170 on Growth of Human LOX Melanoma in  
Athymic Mice: Comparison of Intraperitoneal and Oral Dosing

Treatment	Parameter	Day 0	Day 7	Day 14
Klucel	RTG	1	11.51	40.53
Ex. 170 25 mg/kg bid, ip	RTG	1	4.91	14.77
	T/C	1	0.43	0.36
	p		0.05	0.08
Ex. 170 10 mg/kg bid, ip	RTG	1	8.06	35.55
	T/C		0.70	0.88
	p		0.38	0.53
Ex. 170 25 mg/kg bid, po	RTG	1	10.17	40.49
	T/C		0.88	1.00
	p		0.61	0.53

5

Notes:

1. RTG = relative tumor growth = mean tumor weight on day n/mean tumor weight of same group on day 0. 10 animals in control group, 5 in CL 376894 groups.
- 10 2. Animals were staged on day 0 and dosed on days 1-14.
3. T/C = RTG of treated animals on day n/RTG of control animals on day n.
4. p = p value, Student's T-test.
5. No deaths in experimental groups.

Table 28  
 Evaluation of Example 170 on Growth of Human DLD1 Colon  
 Carcinoma in Athymic Mice: Comparison of Intraperitoneal and  
 Oral Dosing

Treatment	Parameter	Day 0	Day 7	Day 14	Day 21
Klucel	RTG	1	3.17	9.62	18.11
Ex. 170 25 mg/kg bid, ip	RTG	1	3.60	8.08	14.58
	T/C		1.14	0.84	0.81
	p		0.87	0.20	0.31
Ex. 170 25 mg/kg bid, po	RTG	1	3.95	9.64	17.32
	T/C		1.25	1.00	0.96
	p		0.96	0.56	0.48

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Notes:

1. RTG = relative tumor growth = mean tumor weight on day n/mean tumor weight of same group on day 0. Each group had 10 animals.
- 10 2. Animals were staged on day 0 and dosed on days 1-14.
3. T/C = RTG of treated animals on day n/RTG of control animals on day n.
4. p = p value, Student's T-test.
5. No deaths in experimental groups.

Based on the results of these standard pharmacological test procedures, the compounds of this invention are useful as agents for treating, inhibiting or controlling the growth of cancerous tumor cells and associated diseases in a mammal in need thereof by interacting with tubulin and microtubules and

5 promotion of microtubule polymerization. The compounds of the invention are also useful for the treatment or prevention of multiple drug resistant (MDR). The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration and severity of the condition being treated. However, in general satisfactory

10 results are obtained when the compounds of the invention are administered in amounts ranging from about 0.10 to about 100 mg/kg of body weight per day. A preferred regimen for optimum results would be from about 1 mg to about 20 mg/kg of body weight per day and such dosage units are employed that a total of from about 70 mg to about 1400 mg of the active compound for a

15 subject of about 70 kg of body weight are administered in a 24 hour period.

The dosage regimen for treating mammals may be adjusted to provide the optimum therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by

20 the exigencies of the therapeutic situation. A decidedly practical advantage is that these active compounds may be administered in any convenient manner such as by the oral, intravenous, intramuscular or subcutaneous routes. The active compounds may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or they may be enclosed in hard

25 or soft shell gelatin capsules, or they may be compressed into tablets or they may be incorporated directly with the food of the diet. For oral therapeutic administration, these active compounds may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers and the like. Such compositions and

30 preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied

and may conveniently be between about 2% to about 60% of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that a suitable dosage will be obtained. Preferred compositions or preparations according to the present invention are prepared

5 so that an oral dosage unit form contains between 10 and 1000 mg of active compound.

The tablets, troches, pills, capsules and the like may also contain the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose, or saccharin may be added or a flavoring agent such as peppermint, oil of wintergreen or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may

10 be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose, as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in

15 preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts used. In addition, these active compounds may be incorporated into sustained-release preparations and formulations.

20

These active compounds may also be administered parenterally or

25 intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Under ordinary conditions of storage and use, these

30 preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It  
5 must be stable under the conditions of manufacture and storage and must be prepared against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid poly-ethylene glycol), suitable mixtures thereof, and vegetable oils.

10

The following examples are representative compounds of this invention which are useful as promoters of microtubule polymerization and as anticancer agents.

Example 1

15       7-(1-azepanyl)-5-chloro-6-phenyl[1,2,4]triazolo[1,5-a]pyrimidine

Example 2

20       5-chloro-6-(2,6-difluorophenyl)-7-(4-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 3

5-chloro-6-(4-methoxyphenyl)-7-(1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 4

25       5-chloro-6-(2-chloro-6-fluorophenyl)-7-(4-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 5

30       7-(1-azepanyl)-5-chloro-6-(2-chloro-6-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine

### Example 6

**5-chloro-6-(2-chloro-6-fluorophenyl)-7-(2-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine**

### Example 7

**5-chloro-6-(2-chloro-6-fluorophenyl)-7-(4-thiomorpholinyl)[1,2,4]triazolo[1,5-a]pyrimidine**

### Example 8

10 methyl [[5-chloro-6-(2-chloro-6-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-  
y][(methyl)amino]acetate

### Example 9

5-chloro-6-(2-chloro-6-fluorophenyl)-N-(1,1,3,3-tetramethylbutyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

### Example 10

7-(1-azepanyl)-5-chloro-6-(4-methoxyphenyl)[1,2,4]triazolo[1,5-a]pyrimidine

### Example 11

7-(1-azepanyl)-6-(4-bromophenyl)-5-chloro[1,2,4]triazolo[1,5-a]pyrimidine

### Example 12

**5-chloro-7-(1-piperidinyl)-6-[2-(trifluoromethyl)phenyl][1,2,4]triazolo[1,5-  
alpyrimidine**

### Example 13

**6-(4-tert-butylphenyl)-5-chloro-7-(4-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine**

5  
Example 14

5-chloro-6-(4-methoxyphenyl)-7-(4-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine

5  
Example 15

5-chloro-6-(4-methoxyphenyl)-7-(3-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine

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Example 16

6-(4-bromophenyl)-5-chloro-7-(3-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine

15  
Example 17

5-chloro-6-(3,4-difluorophenyl)-7-(4-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine

20  
Example 18

5-chloro-6-(2,6-dichlorophenyl)-7-(2-methyl-1-pyrrolidinyl)[1,2,4]triazolo[1,5-a]pyrimidine

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Example 19

5-chloro-6-(2-chlorophenyl)-7-(2-methyl-1-pyrrolidinyl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 20

7-(1-azepanyl)-5-chloro-6-(3-chloro-4-methoxyphenyl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 21

5-chloro-6-(3-chloro-4-methoxyphenyl)-7-(4-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 22

5-chloro-6-(3-chloro-4-methoxyphenyl)-7-(2-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 23

10      6-(4-tert-butylphenyl)-5-chloro-7-(2-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 24

15      5-chloro-7-(2-methyl-1-piperidinyl)-6-[3-(trifluoromethyl)phenyl][1,2,4]triazolo[1,5-a]pyrimidine

Example 25

20      Diethyl 2-[6-(2,6-difluorophenyl)-5-ethoxy[1,2,4]triazolo[1,5-a]pyrimidin-7-yl]malonate

Example 26

7-(azepanyl)-5-chloro-6-(2-chloro-6-nitrophenyl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 27

25      5-chloro-6-(2-chloro-6-fluorophenyl)-N-ethyl-N-(2-methyl-2-propenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

Example 28

30      5-chloro-6-(2-chloro-6-fluorophenyl)-N-(2,2,2-trifluoroethyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

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Example 29

5-chloro-6-(2-chloro-6-fluorophenyl)-N-[(2,2-dichlorocyclopropyl)methyl]-N-methyl[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

5  
Example 30

1-[5-chloro-6-(2-chloro-6-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-yl]-3-piperidinol

10  
Example 31

N-bicyclo[2.2.1]hept-2-yl-5-chloro-6-(3-chloro-4-methoxyphenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

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Example 32

5-chloro-6-(2,5-difluorophenyl)-N-dodecyl[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

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Example 33

5-chloro-7-(4-methyl-1-piperidinyl)-6-(2,3,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine

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Example 34

N-[5-chloro-6-(2,3,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-yl]-N-isopropylamine

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Example 35

5-chloro-N-ethyl-N-(2-methyl-2-propenyl)-6-(2,3,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

Example 36

N-allyl-5-chloro-6-(2-chloro-6-fluorophenyl)-N-(2-methyl-2-propenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

Example 37

5-chloro-6-(2-chloro-6-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

Example 38

5  
5-chloro-6-(3-chloro-4-methoxyphenyl)-N-cycloheptyl[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

Example 39

10  
5-chloro-6-(3-chloro-4-methoxyphenyl)-7-(3,3-dimethyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 40

15  
5-chloro-N-(3-chloropropyl)-N-methyl-6-(2,3,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

Example 41

7-(1-azocanyl)-5-chloro-6-(2,3,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 42

20  
5-chloro-6-(2,6-difluorophenyl)-7-(3,6-dihydro-1(2H)-pyridinyl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 43

25  
7-(1-azocanyl)-5-chloro-6-(2,6-difluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 44

5-methoxy-6-(2-chloro-6-fluorophenyl)-7-(4-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 45

[5-chloro-6-(2-chloro-6-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-y]methanol

Example 46

1-[5-chloro-6-(2,6-difluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-y]4-piperidinol

Example 47

10 5-chloro-7-(4-chloro-1-piperidinyl)-6-(2,6-difluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 48

15 5-chloro-7-(4-thiomorpholinyl)-6-(2,3,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 49

20 5-chloro-6-(2,6-difluorophenyl)-7-(2,4-dimethyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 50

7-(4-methyl-1-piperidinyl)-5-amino-6-(2-chloro-6-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 51

25 5-chloro-6-(2,6-difluorophenyl)-7-(2,5-dihydro-1H-pyrrol-1-yl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 52

30 5-chloro-6-(2-chloro-6-fluorophenyl)-7-(2,5-dimethyl-2,5-dihydro-1H-pyrrol-1-yl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 53

5-chloro-6-(2-chloro-6-fluorophenyl)-7-(2-ethyl-1H-imidazol-1-  
y) [1,2,4]triazolo[1,5-a]pyrimidine

Example 54

7-(4-bromo-1-piperidinyl)-5-chloro-6-(2-chloro-6-  
fluorophenyl) [1,2,4]triazolo[1,5-a]pyrimidine

Example 55

10 5-chloro-6-(2-methylphenyl)-7-(4-thiomorpholinyl) [1,2,4]triazolo[1,5-  
a]pyrimidine

Example 56

15 6-(2-bromophenyl)-N-(sec-butyl)-5-chloro [1,2,4]triazolo[1,5-a]pyrimidin-7-  
amine

Example 57

20 5-chloro-N-ethyl-6-(4-methoxyphenyl)-N-(2-methyl-2-  
propenyl) [1,2,4]triazolo[1,5-a]pyrimidin-7-amine

Example 58

5-chloro-6-(4-methoxyphenyl)-7-(4-thiomorpholinyl) [1,2,4]triazolo[1,5-  
a]pyrimidine

Example 59

25 5-chloro-7-(4-chloro-1-piperidinyl)-6-[2-  
(trifluoromethyl)phenyl] [1,2,4]triazolo[1,5-a]pyrimidine

Example 60

30 5-chloro-6-(2-chloro-6-fluorophenyl)-7-[4-(trifluoromethyl)-1-  
piperidinyl] [1,2,4]triazolo[1,5-a]pyrimidine

Example 61

7-(4-bromo-1-piperidinyl)-5-chloro-6-(2,6-difluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 62

7-(4-bromo-1-piperidinyl)-5-chloro-6-(2-chlorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 63

10 5-chloro-N-ethyl-N-(2-methyl-2-propenyl)-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

Example 64

15 5-chloro-N-isopropyl-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

Example 65

20 5-chloro-7-(4-thiomorpholinyl)-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 66

7-(1-azepanyl)-5-chloro-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 67

25 5-chloro-6-(2-chloro-6-fluorophenyl)-7-[2-(1-pyrrolidinyl)-1-cyclopenten-1-yl][1,2,4]triazolo[1,5-a]pyrimidine

Example 68

30 5-chloro-7-(4-isopropyl-1-piperidinyl)-6-(4-methoxyphenyl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 69

5-chloro-7-(2,4-dimethyl-1-piperidinyl)-6-(4-methoxyphenyl)[1,2,4]triazolo[1,5-a]pyrimidine

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Example 70

5-chloro-7-[ethyl(2-methyl-2-propenyl)amino]-6-{4-nitrophenyl}[1,2,4]triazolo[1,5-a]pyrimidine

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Example 71

7-(1-azepanyl)-5-chloro-6-{4-nitrophenyl}[1,2,4]triazolo[1,5-a]pyrimidine

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Example 72

N-bicyclo[2.2.1]hept-2-yl-5-chloro-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

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Example 73

5-chloro-6-(2,6-difluorophenyl)-N-(2,2,2-trifluoroethyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

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Example 74

5-chloro-6-(2-chlorophenyl)-N-(2,2,2-trifluoroethyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

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Example 75

5-chloro-6-(2-chloro-6-fluorobenzyl)-7-tetrahydro-2-furanyl[1,2,4]triazolo[1,5-a]pyrimidine

Example 76

7-(allylsulfanyl)-5-chloro-6-(2-chloro-6-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 77

5-chloro-N-ethyl-6-mesityl-N-(2-methyl-2-propenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

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Example 78

5-chloro-N-ethyl-6-(2-methoxyphenyl)-N-(2-methyl-2-propenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

10

Example 79

5-chloro-6-(2-chloro-6-fluorophenyl)-N-hexyl[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

15

Example 80

5-chloro-7-(4-methyl-1-piperidinyl)-6-[4-(methylsulfanyl)phenyl][1,2,4]triazolo[1,5-a]pyrimidine

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Example 81

5-chloro-N-ethyl-N-(2-methyl-2-propenyl)-6-[4-(methylsulfanyl)phenyl][1,2,4]triazolo[1,5-a]pyrimidin-7-amine

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Example 82

N-(sec-butyl)-5-chloro-6-[4-(methylsulfanyl)phenyl][1,2,4]triazolo[1,5-a]pyrimidin-7-amine

Example 83

5-chloro-6-[4-(methylsulfanyl)phenyl]-7-(4-thiomorpholinyl)[1,2,4]triazolo[1,5-a]pyrimidine

#### Example 84

5-chloro-6-[2,6-dichloro-4-(trifluoromethyl)phenyl]-7-(4-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine

### Example 85

7-(1-azepanyl)-5-chloro-6-[2,6-dichloro-4-(trifluoromethyl)phenyl][1,2,4]triazolo[1,5-a]pyrimidine

### Example 86

5-chloro-6-(2-chloro-6-fluorophenyl)-7-[(2,2,2-trifluoroethyl)sulfanyl][1,2,4]triazolo[1,5-a]pyrimidine

### Example 87

5-chloro-6-(2-chloro-6-fluorophenyl)-7-(4,4-dimethyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine

### Example 88

**5-chloro-6-[2,6-dichloro-4-(trifluoromethyl)phenyl]-N-ethyl-N-(2-methyl-2-propenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine**

### Example 89

5-chloro-6-[2,6-dichloro-4-(trifluoromethyl)phenyl]-7-(4-thiomorpholinyl)[1,2,4]triazolo[1,5-a]pyrimidine

### Example 90

**5-chloro-6-(3,5-difluorophenyl)-7-(4-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine**

### Example 91

**a]pyrimidine**

### Example 92

**5-chloro-6-(2-chloro-6-fluorophenyl)-7-tetrahydro-2-furanyl[1,2,4]triazolo[1,5-a]pyrimidine**

### Example 93

4-[5-chloro-7-(4-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidin-6-yl]aniline

### Example 94

**N-[4-[5-chloro-7-(4-methyl-1-piperidinyl)]1,2,4]triazolo[1,5-a]pyrimidin-6-yl]phenyl}acetamide**

### Example 95

15 [5-chloro-6-(2-chloro-6-fluorophenyl)][1,2,4]triazolo[1,5-a]pyrimidin-7-yl)methyl acetate

### Example 96

**5-chloro-6-(2-chloro-6-fluorophenyl)-7-(chloromethyl)[1,2,4]triazolo[1,5-a]pyrimidine**

### Example 97

diethyl 2-[6-(2-chloro-6-fluorophenyl)-7-(4-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidin-5-yl]malonate

### Example 98

7-(1-azepanyl)methyl)-5-chloro-6-(2-chloro-6-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 99

N-allyl-5-chloro-6-(2-chloro-6-fluorophenyl)-N-hexyl[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

Example 100

5-chloro-7-(4-methyl-1-piperidinyl)-6-[4-(trifluoromethoxy)phenyl][1,2,4]triazolo[1,5-a]pyrimidine

Example 101

10 5-chloro-7-(4-methyl-1-piperidinyl)-6-(4-phenoxyphenyl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 102

15 5-chloro-6-(2-chloro-6-fluorophenyl)-N-(cyclopropylmethyl)-N-propyl[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

Example 103

20 5-chloro-7-(2-methyl-1-piperidinyl)-6-(4-phenoxyphenyl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 104

5-chloro-6-(2-chloro-4-nitrophenyl)-7-(4-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 105

25 5-chloro-6-(4-chloro-2,3,5,6-tetrafluorophenyl)-N-cyclopentyl[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

Example 106

30 4-[5-chloro-2-methyl-7-(4-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidin-6-yl]-N,N-dimethylaniline

5                   Example 107

6-(2-chloro-6-fluorophenyl)-5-methyl-7-(4-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine

5                   Example 108

5-chloro-6-(2-chloro-6-fluorophenyl)-7-[2-(1-pyrrolidinyl)-1-cyclohexen-1-yl][1,2,4]triazolo[1,5-a]pyrimidine

10                  Example 109

5-chloro-6-(2-chloro-6-fluorophenyl)-7-(methoxymethyl)[1,2,4]triazolo[1,5-a]pyrimidine

15                  Example 110

5-chloro-6-[2-chloro-4-nitrophenyl]-7-[ethyl(2-methyl-2-propenyl)amino][1,2,4]triazolo[1,5-a]pyrimidine

20                  Example 111

5-bromo-6-(2-chloro-6-fluorophenyl)-7-(isopropylsulfanyl)[1,2,4]triazolo[1,5-a]pyrimidine

25                  Example 112

5-chloro-N-cyclopentyl-6-(4-ethoxy-2,3,5,6-tetrafluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

30                  Example 113

5-chloro-N-methyl-N-(2-methyl-2-propenyl)-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

Example 114

4-bromo-1-[5-chloro-6-(2-chloro-6-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-yl]butyl acetate

5                   Example 115

diethyl 2-allyl-2-{[5-chloro-6-(2-chloro-6-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-yloxy]malonate}

10                  Example 116

6-(2-chloro-6-fluorophenyl)-N-ethyl-5-methyl[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

15                  Example 117

N-butyl-5-chloro-N-ethyl-6-(2,3,4,5,6-pentafluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

20                  Example 118

6-(2-chloro-6-fluorophenyl)-5-(difluoromethoxy)-7-(4-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine

25                  Example 119

5-chloro-6-(2-chloro-6-fluorophenyl)-7-[(4-chlorophenyl)sulfanyl][1,2,4]triazolo[1,5-a]pyrimidine

30                  Example 120

5-chloro-6-(2-chloro-6-fluorophenyl)-7-[(2-methoxyphenyl)sulfanyl][1,2,4]triazolo[1,5-a]pyrimidine

25                  Example 121

5-chloro-6-(2-chloro-6-fluorophenyl)-N-(1,2,2-trimethylpropyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

30                  Example 122

5-chloro-6-(2,3,4,5,6-pentafluorophenyl)-N-(1,2,2-trimethylpropyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

### Example 123

**5-chloro-6-(2,4,6-trifluorophenyl)-N-(1,2,2-trimethylpropyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine**

### Example 124

**5-chloro-6-(4-fluorophenyl)-N-(1,2,2-trimethylpropyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine**

### Example 125

10 5,7-bis(4-methyl-1-piperidinyl)-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine

### Example 126

**5-chloro-6-(2-methylphenyl)-N-(1,2,2-trimethylpropyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine**

### Example 127

**5-chloro-6-(2,4,5-trifluorophenyl)-N-(1,2,2-trimethylpropyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine**

### Example 128

**6-(2-bromophenyl)-5-chloro-N-(1,2,2-trimethylpropyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine**

### Example 129

5-chloro-N-isobutyl-N-(2,2,2-trifluoroethyl)-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1.5-a]pyrimidin-7-amine

### Example 130

5-chloro-N-isobutyl-6-(2-methylphenyl)-N-(2,2,2-trifluoroethyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

5  
Example 131

5-chloro-6-(2-chloro-6-fluorophenyl)-N-(2,2,2-trifluoro-1-methylethyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

10  
Example 132

5-chloro-6-(2,6-difluorophenyl)-N-(2,2,2-trifluoro-1-methylethyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

15  
Example 133

5-chloro-N-(2,2,2-trifluoro-1-methylethyl)-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

20  
Example 134

N-allyl-5-chloro-N-isobutyl-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

25  
Example 135

5-chloro-N-(1,2-dimethylpropyl)-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

30  
Example 136

5-chloro-N-isopropyl-N-methyl-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

35  
Example 137

5-chloro-N-isopropyl-N-(2,2,2-trifluoroethyl)-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

Example 138

7-butyl-5-chloro-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 139

5      5-chloro-N-(1-phenylethyl)-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

Example 140

10     5-chloro-6-(2-chlorophenyl)-N-(2,2,2-trifluoro-1-methylethyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

Example 141

15     5-chloro-N-ethyl-N-isobutyl-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

Example 142

5-chloro-6-(2-chloro-6-fluorophenyl)-7-hexyl[1,2,4]triazolo[1,5-a]pyrimidine

Example 143

20     5-chloro-6-(2-methylphenyl)-N,N-bis(2,2,2-trifluoroethyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

Example 144

25     5-chloro-N-cyclopentyl-N-methyl-6-(2,3,4,5,6-pentafluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

Example 145

7-butyl-5-chloro-6-(2,6-difluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 146

5-chloro-N-(1,2-dimethylpropyl)-N-methyl-6-(2,3,4,5,6-pentafluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

5

Example 147

5-chloro-6-(2-chloro-6-fluorophenyl)-7-phenyl[1,2,4]triazolo[1,5-a]pyrimidine

10

Example 148

5-chloro-6-(2-chloro-6-fluorophenyl)-7-(2-methylpropyl)[1,2,4]triazolo[1,5-a]pyrimidine

15

Example 149

5-chloro-6-(2-chloro-6-fluorophenyl)-7-pentyl[1,2,4]triazolo[1,5-a]pyrimidine

20

Example 150

5-chloro-N-(1,2-dimethylpropyl)-N-methyl-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

25

Example 151

5-chloro-6-(2-chloro-6-fluorophenyl)-7-cyclohexyl[1,2,4]triazolo[1,5-a]pyrimidine

Example 152

5-chloro-6-(2-bromo-5-chlorophenyl)-N-(2,2,2-trifluoro-1-methylethyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

Example 153

5-chloro-6-(2-chloro-6-fluorophenyl)-7-(3,3,3-trifluoropropyl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 154

5-chloro-6-(2-chloro-6-fluorophenyl)-7-(3-methylphenyl)[1,2,4]triazolo[1,5-a]pyrimidine

5

Example 155

[5-chloro-6-(2,4,6-trifluorophenyl)-1,2,4]triazolo[1,5-a]pyrimidin-7-yl]-{(1-p-tolyl-  
ethyl)-amine}

10

Example 156

5-chloro-6-(2,4,6-trifluoro-phenyl)-7-cyclohexyl[1,2,4]triazolo[1,5-a]pyrimidine

15

Example 157

5-chloro-7-cyclohexyl-6-(2,3,4,5,6-pentafluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine

20

Example 158

5-chloro-6-(2-chloro-6-fluorophenyl)-7-(4,4-difluoro-1-  
piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine

25

Example 159

7-(bicyclo[2.2.1]hept-2-ylamino)-5-chloro-6-{2-fluoro-4-  
nitrophenyl}[1,2,4]triazolo[1,5-a]pyrimidine

Example 160

5-chloro-6-{2-fluoro-4-nitrophenyl}-7-(4-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine

30

Example 161

5-(methylsulfanyl)-6-(2-chloro-6-fluorophenyl)-7-cyclohexyl[1,2,4]triazolo[1,5-a]pyrimidine

Example 162

[5-chloro-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-yl] (2,2,2-trifluoro-1-phenylethyl)-amine

5 Example 163

5-chloro-N-[1-(trifluoromethyl)propyl]-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

10 Example 164

5-bromo-6-(2-chloro-6-fluorophenyl)-7-cyclohexyl[1,2,4]triazolo[1,5-a]pyrimidine

15 Example 165

6-(2-chloro-6-fluorophenyl)-7-cyclohexyl[1,2,4]triazolo[1,5-a]pyrimidin-5-amine

15 Example 166

[5-chloro-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-yl]-(2-methyl-1-trifluoromethyl-propyl)amine

20 Example 167

5-chloro-7-(3-cyclohexen-1-yl)-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 168

25 5-chloro-7-(1-cyclohexen-1-yl)-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 169

30 5-chloro-N-[(1R)-2,2,2-trifluoro-1-methylethyl]-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

Example 170

5-chloro-N-[(1R)-2,2,2-trifluoro-1-methylethyl]-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

Example 171

6-(2,4-difluorophenyl)-5-chloro-N-(2,2,2-trifluoro-1-methylethyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

Example 172

5-chloro-6-(2,6-difluoro-4-methoxyphenyl)-7-(4-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 173

5-chloro-6-(2,6-difluoro-4-methoxyphenyl)-N-(2,2,2-trifluoro-1-methylethyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

Example 174

5-chloro-7-cyclohexyl-6-(2,6-difluoro-4-methoxyphenyl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 175

5-chloro-6-(2,6-difluoro-4-methoxyphenyl)-N-[(1S)-2,2,2-trifluoro-1-methylethyl][1,2,4]triazolo[1,5-a]pyrimidin-7-amine

Example 176

7-cyclohexyl-6-(2,6-difluoro-4-methoxyphenyl)-5-methoxy[1,2,4]triazolo[1,5-a]pyrimidine

Example 177

5-chloro-7-(4-fluorocyclohexyl)-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine

### Example 178

5-chloro-6-(2,6-dichloro-4-fluorophenyl)-7-(3,3,3-trifluoropropyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

### Example 179

**N-(sec-butyl)-5-chloro-6-(2,6-dichloro-4-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine**

### Example 180

**4-[5-chloro-7-[(2,2,2-trifluoro-1-methylethyl)amino][1,2,4]triazolo[1,5-a]pyrimidin-6-yl]-3,6-difluorophenol**

### Example 181

**5-chloro-7-(3-cyclohexen-1-yl)-6-(2,6-difluoro-4-methoxyphenyl)[1,2,4]triazolo[1,5-a]pyrimidine**

### Example 182

**5-chloro-6-(2,6-difluoro-4-methoxyphenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine**

### Example 183

**5-chloro-N-cyclopentyl-6-(2,6-difluoro-4-methoxyphenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine**

### Example 184

5-chloro-6-(2,6-difluoro-4-methoxyphenyl)-7-(3,6-dihydro-1(2H)-pyridinyl)[1,2,4]triazolo[1,5-a]pyrimidine

### Example 185

**5-chloro-6-(2,6-difluoro-4-methoxyphenyl)-7-(4-thiomorpholinyl)[1,2,4]triazolo[1,5-a]pyrimidine**

Example 186

7-(1-azepanyl)-5-chloro-6-(2,6-difluoro-4-methoxyphenyl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 187

5-chloro-6-(2,6-difluoro-4-methoxyphenyl)-N-(1,2,2-trimethylpropyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

Example 188

10 5-chloro-6-(2,6-difluoro-4-methoxyphenyl)-N-ethyl-N-(2-methyl-2-propenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

Example 189

15 5-chloro-6-(2,6-difluoro-4-methoxyphenyl)-7-(4-fluorocyclohexyl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 190

6-(4-{5-chloro-7-[(2,2,2-trifluoro-1-methylethyl)amino][1,2,4]triazolo[1,5-a]pyrimidin-6-yl}-3,5-difluorophenoxy)hexanoic acid

Example 191

2,6-difluoro-4-(2-fluoroethoxy)phenyl-N-(2,2,2-trifluoro-1-methylethyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

Example 192

25 5-chloro-N-isopropyl-6-[2-[(trifluoromethyl)sulfanyl]phenyl][1,2,4]triazolo[1,5-a]pyrimidin-7-amine

Example 193

30 5-chloro-N-[4-(trifluoromethyl)phenyl]-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

Example 194

5-chloro-N-(4,4,4-trifluoro-2-methylbutyl)-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

5 Example 195

5-chloro-6-(2,6-difluoro-4-methoxyphenyl)-7-(3-methyl-3-but enyl)[1,2,4]triazolo[1,5-a]pyrimidine

10 Example 196

5-chloro-6-(2,6-difluoro-4-methoxyphenyl)-7-isobutyl[1,2,4]triazolo[1,5-a]pyrimidine

15 Example 197

7-cyclopentyl-6-(2,6-difluoro-4-methoxyphenyl)-5-methoxy[1,2,4]triazolo[1,5-a]pyrimidine

20 Example 198

5-chloro-6-(2-thienyl)-N-[(1R)-2,2,2-trifluoro-1-methylethyl][1,2,4]triazolo[1,5-a]pyrimidin-7-amine

Example 199

4-(5-chloro-7-(2,2,2-trifluoro-1-methyl-ethylamino)[1,2,4]triazolo[1,5-a]pyrimidin-6-yl]-3,5-difluoro-phenol

25 Example 200

{5-chloro-6-[2,6-difluoro-4-(2,2,2-trifluoro-ethoxy)-phenyl]-[1,2,4]triazolo[1,5-a]pyrimidin-7-yl}-(2,2,2-trifluoro-1-methyl-ethyl)amine

Example 201

5-chloro-6-[2,6-difluoro-4-(methoxyphenyl)-N-(2,2,2-trifluoro-1-methylethyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

5                   **Example 202**

(5-chloro-6-(4-[2-(2-ethoxyethoxy)-ethoxy]-2,6-difluoro-phenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-yl)-(2,2,2-trifluoro-1-methylethyl)amine

10                  **Example 203**

(5-chloro-6-(2,6-difluoro-4-[2-(2-methoxy-ethoxy)ethoxy]-phenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-yl)-(2,2,2-trifluoro-1-methylethyl)amine

15                  **Example 204**

5-chloro-6-[2,6-difluoro-4-(3-furan-3-ylmethoxy)phenyl][1,2,4]triazolo[1,5-a]pyrimidin-7-yl]-N-(2,2,2-trifluoro-1-methylethyl)amine

20                  **Example 205**

5-chloro-6-(2,5-difluoro-4-methoxyphenyl)-N-(1,2,2-trimethylpropyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

25                  **Example 206**

7-cyclohexyl-6-[2,6-difluoro-4-(2-methoxyethoxy)phenyl]-5-methoxy[1,2,4]triazolo[1,5-a]pyrimidine

30                  **Example 207**

5-chloro-6-(2-fluoro-4-methoxy-6-chlorophenyl)-N-(2,2,2-trifluoro-1-methylethyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

35                  **Example 208**

5-chloro-6-[2,6-difluoro-4-(2-fluoroethoxy)phenyl]-N-ethyl-N-(2-methyl-2-propenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

### Example 209

2-[2-(4-{5-chloro-7-[(2,2,2-trifluoro-1-methylethyl)amino][1,2,4]triazolo[1,5-a]pyrimidin-6-yl]-3,5-difluorophenoxy)ethoxy]ethanol

### Example 210

5-chloro-6-(2,3-difluoro-4-methoxyphenyl)-N-(2,2,2-trifluoro-1-methylethyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

### Example 211

10 **5-chloro-6-[4-(2-fluoroethoxy)-2,6-difluorophenyl]-N-(2,2,2-trifluoro-1-methylethyl)[1,2,4]triazolo[1.5-a]pyrimidin-7-amine**

### Example 212

**5-chloro-N-(4-chlorobenzyl)-6-(2-chloro-6-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine**

### Example 213

5-chloro-6-(2-chloro-6-fluorophenyl)-7-[4-(2-pyridinyl)-1-piperazinyl][1,2,4]triazolo[1,5-a]pyrimidine

#### Example 214

**5-chloro-6-(2-chloro-6-fluorophenyl)-N-(1-ethylpentyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine**

### Example 215

**5-chloro-6-(2-chloro-6-fluorophenyl)-7-[4-(2-chlorophenyl)-1-piperazinyl]1,2,4-triazolo[1,5-a]pyrimidine**

### Example 216

30 5-chloro-6-(2-chloro-6-fluorophenyl)-7-[4-(4-methoxyphenyl)-3-methyl-1-  
piperazinyl] [1,2,4]triazolo[1,5-a]pyrimidine

5  
Example 217

5-chloro-N-cyclopentyl-6-(2-chloro-6-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

10  
Example 218

5-chloro-7-phenoxy-6-(4-methoxy-phenyl)[1,2,4]triazolo[1,5-a]pyrimidine

15  
Example 219

5-chloro-N-cyclopentyl-6-(4-methylphenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

20  
Example 220

5,7-diphenoxy-6-(4-methoxyphenyl)[1,2,4]triazolo[1,5-a]pyrimidine

25  
Example 221

5-chloro-N-cyclopentyl-6-(2-chlorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

30  
Example 222

5-chloro-N,N-diethyl-6-[4-methoxyphenyl][1,2,4]triazolo[1,5-a]pyrimidin-7-amine

35  
Example 223

5-chloro-N,N-diethyl-6-[2,4-dichlorophenyl][1,2,4]triazolo[1,5-a]pyrimidin-7-amine

40  
Example 224

N-bicyclo[2.2.1]hept-2-yl-5-chloro-6-(2,4-dichlorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

5  
Example 225

5-chloro-6-(2-chloro-6-fluorophenyl)-7-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)[1,2,4]triazolo[1,5-a]pyrimidine

10  
Example 226

5-cyano-7-(4-methyl-1-piperidinyl)-6-(2-chloro-5-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine

15  
Example 227

5-(methylsulfanyl)-7-(4-methyl-1-piperidinyl)-6-(2-chloro-6-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine

20  
Example 228

5-(methylsulfanyl)-7-(4-methyl-1-piperidinyl)-6-(2-chloro-5-(methylsulfanyl)phenyl)[1,2,4]triazolo[1,5-a]pyrimidine

25  
Example 229

5-chloro-7-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-6-(4-methoxyphenyl)[1,2,4]triazolo[1,5-a]pyrimidine

30  
Example 230

5-chloro-N-ethyl-N-(2-methyl-2-propenyl)-6-(4-(methylsulfanyl)phenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

25  
Example 231

2-methyl-6,7-di-(4-methoxyphenyl)[1,2,4]triazolo[1,5-a]pyrimidine

30  
Example 232

2-methyl-6-phenyl-7-(4-chlorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 233

2-trifluoromethyl-6-phenyl-7-(4-methoxyphenyl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 234

5       5,7-diphenoxy-6-(2-methylpropyl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 235

10      5-chloro-6-(3,4-difluorophenyl)-N-(isopropyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

Example 236

5-bromo-6-(4-bromophenyl)-7-dimethylamino[1,2,4]triazolo[1,5-a]pyrimidine

Example 237

15      5-bromo-6-(4-trifluoromethylphenyl)-7-dimethylamino[1,2,4]triazolo[1,5-a]pyrimidine

Example 238

5-chloro-6-(3,4-difluorophenyl)-7-dimethylamino[1,2,4]triazolo[1,5-a]pyrimidine

Example 239

20      5-chloro-6-(4-trifluoromethylphenyl)-N-(ethyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

Example 240

7-(1-azepanyl)-5-chloro-6-(4-tert-butylphenyl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 241

25      ethyl {[5-chloro-6-(2-chloro-6-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-yl]amino}acetate

5  
Example 242

diethyl 5-chloro-6-(2,6-difluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-malonate

5  
Example 243

5-chloro-6-(2,5-difluorophenyl)-N-(3-methyl-2-butenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

10  
Example 244

[5-chloro-6-(2-chloro-6-fluorophenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-7-yl]acetic acid methyl ester

15  
Example 245

5-chloro-6-(2,6-difluorophenyl)-7-(2-ethyl-1H-imidazol-1-yl)[1,2,4]triazolo[1,5-a]pyrimidine

20  
Example 246

5-chloro-N,N-diethyl-6-[4-(methylsulfanyl)phenyl][1,2,4]triazolo[1,5-a]pyrimidin-7-amine

25  
Example 247

ethyl [6-(2-chloro-6-fluorophenyl)-7-(4-methyl-1-piperidinyl)-[1,2,4]triazolo[1,5-a]pyrimidin-5-yl]acetate

30  
Example 248

5-chloro-N-ethyl-N-(2-methyl-2-propenyl)-6-(4-phenoxyphenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

Example 249

dimethyl 2-[5-chloro-6-(2-chloro-6-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-yl]malonate

Example 250

diethyl 2-([5-chloro-6-(2-chloro-6-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-yl]oxy)-2-isobutylmalonate

Example 251

2-[5-chloro-6-(2-chloro-6-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-yl]-1,3-cyclohexanedione

Example 252

2-[5-chloro-6-(2-chloro-6-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-yl]cyclohexanone

Example 253

5-chloro-7-(3-nitro-4-methylanilino)-6-(2, 4, 6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 254

7-cyclohexyl-6-[2,6-difluoro-4-(2-methoxyethoxy)phenyl]5-(2-methoxyethoxy)[1,2,4]triazolo[1,5-a]pyrimidine

Example 255

7-(3-bromophenyl)-2-ethyl-6-(4-methoxyphenyl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 256

7-(3-bromophenyl)-6-(3-chlorophenyl)-2-ethyl[1,2,4]triazolo[1,5-a]pyrimidine

Example 257

7-(4-bromophenyl)-2-ethyl-6-[4-(trifluoromethyl)phenyl][1,2,4]triazolo[1,5-a]pyrimidine

5                   **Example 258**

5-chloro-6-(2-chloro-6-fluorophenyl)-N-(3,4,5-trimethoxybenzyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

5                   **Example 259**

7-(2-benzyl-4,5-dihydro-1H-imidazol-1-yl)-5-chloro-6-(2-chloro-6-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine

10                  **Example 260**

N-4-[5-chloro-6-(2-chloro-6-fluorophenyl)][1,2,4]triazolo[1,5-a]pyrimidin-7-yl-N,N-1-diethyl-1,4-pentanediamine

15                  **Example 261**

5-chloro-N-(3-methyl-2-butenyl)-6-phenyl[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

20                  **Example 262**

5-dimethylamino-6-phenyl-N-cyclopentyl[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

25                  **Example 263**

5-chloro-7-[(2-furylmethyl)sulfanyl]-6-(4-methoxyphenyl)[1,2,4]triazolo[1,5-a]pyrimidine

30                  **Example 264**

6-[1,1'-biphenyl]-4-yl-5-chloro-N-cyclopentyl[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

35                  **Example 265**

6-[4-(benzyloxy)phenyl]-5-chloro-N-isopropyl[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

Example 266

5-chloro-N-[(2,2-dichlorocyclopropyl)methyl]-6-(3,4,5-trimethoxyphenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

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Example 267

N-cyclopentyl-6-(2-fluorophenyl)-5-hydrazino[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

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5-chloro-N-ethyl-6-(2-methylphenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

Example 269

6-(4-tert-butylphenyl)-5-chloro-N-isopropyl[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

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Example 270

5-chloro-6-[2,6-difluoro-4-[(3-methyl-2-butenyl)oxy]phenyl]-N-(2,2,2-trifluoro-1-methylethyl)-[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

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Example 271

5-chloro-6-[2,6-difluoro-4-(1-propenoxy)phenyl]-N-(2,2,2-trifluoro-1-methylethyl)-[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

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Example 272

5-chloro-N-(3-tricyclo[2.2.1.0<sup>2,6</sup>]hept-1-yl)-6-(2,4,6-trifluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-amine

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Example 273

5-azido-7-cyclohexyl-6-(2-fluoro-6-chlorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine

Example 274

5-azido-6-[2-chloro-6-fluorophenyl]-7-(4-methyl-1-piperidinyl)[1,2,4]triazolo[1,5-a]pyrimidine

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Example 275

2,5-dichloro-7-(4-methyl-1-piperidinyl)-6-[2-chloro-6-fluorophenyl][1,2,4]triazolo[1,5-a]pyrimidine

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